ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 18 December, 1960 Number 12

DEPO-METHYLPREDNISOLONE IN THE TREATMENT OF RAGWEED HAYFEVER

EARL BROWN, M.D., THOMAS SEIDEMAN, M.D.,
A. B. SIEGELAUB, B.B.A., and CHARLES POPOVITZ, M.D., F.A.C.A.

New York, New York

WHILE oral methylprednisolone is effective[1] in the treatment of ragweed pollinosis, it has the disadvantage which characterizes all oral corticosteroids in that it elicits a high percentage of gastro-intestinal discomfort. West[2] has suggested that gastritis is the result of local action of the medication on the gastric mucosa. Since depo-methylprednisolone* by-passes the gastric mucosa, the incidence of gastritis and ulcers as a result of steroid therapy might be lessened. Another advantage of parenteral medication is that it gives the physician full control of the dosage of this potent medication. The study was conducted on a double blind basis in order to evaluate the effectiveness and side reactions of this medication adequately.

TABLE I. COMPOSITION OF DOUBLE-BLIND STUDY

Treatment	Number of Patients	Female	Male	Average Age in Years	Per Cent on Full Course of 3 Injections
6-methylprednisolone acetate	50	30	20	34.0	86.0
Placebo control	45	20	25	29.0	77.8
	95	50	45	31.6	82.1

For comparisons, the probability of difference between the active drug and placebo control is not significant at .05 level.

METHODS AND MATERIALS

Ninety-five patients who had responded poorly to courses of hyposensitization or had received no previous treatment were studied. In all

From the Division of Medicine and Social Medicine, Montefiore Hospital, New York, N. Y.

*Furnished as Depo-Medrol® by the Medical Research Department of the Upjohn Pharmaceutical Company, Kalamazoo, Michigan.

DAILY RECORD OF SYMPTOMS

MONTH OF_____ 19_____

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Severe Hay Fever																															
Moderate Hay Fever																															
Slight Hay Fever																															
No Hay Fever																															
Other Medication																															

MONTH OF_____

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Severe Hay Fever																															
Moderate Hay Fever																															
Slight Hay Fever																															
No Hay Fever																															
Other Medication																															

Severe Hay Fever means practically continuous symptoms. **Moderate Hay Fever**—symptoms lasting a total of 2-4 hours in a day. **Slight Hay Fever**—symptoms lasting 15 minutes to 2 hours.

HAY FEVER SYMPTOMS: EYE OR NOSE ITCHING, SNEEZING AND/OR NOSE RUNNING AND NASAL CLOGGING.

Fig. 1. Daily record of symptoms

cases, the diagnosis of ragweed pollinosis was confirmed by history and by intracutaneous tests. Hyposensitization therapy was continued throughout the study in those patients who had been seen antecedent to June, 1959. Of these ninety-five patients, fifty received depo-methylprednisolone and forty-five received the placebo. Dosage was 80 mgm weekly, given intramuscularly in the gluteus maximus. Each 1 ml contained the following:

Methylprednisolone acetate, 40 mgm
Polyethylene glycol, 4000, U.S.P. XV
Sodium Chloride, U.S.P. XV
Myristyle-gamma-picolinium Chloride
Water for injection, U.S.P. XV

TABLE II. REPORTED SYMPTOMS BY SIX-DAY PERIODS

Per Cent

	Depo-methyl-prednisolone	Control	Probability of Difference*
1st period, N—100 per cent	192	159	
No symptoms	27	8	.001
Slight or moderate	65	72	Significant
Severe symptoms	8	20	
2nd period, N—100 per cent	259	223	
No symptoms	34	6	.001
Slight or moderate	59	71	Significant
Severe symptoms	7	23	
3rd period, N—100 per cent	268	227	
No symptoms	41	13	.001
Slight or moderate	55	71	Significant
Severe symptoms	4	16	
4th period, N—100 per cent	187	162	
No symptoms	53	11	.001
Slight or moderate	45	78	Significant
Severe symptoms	2	21	
5th period, N—100 per cent	70	59	
No symptoms	74	27	.001
Slight or moderate	26	49	Significant
Severe symptoms	0	24	

*Probability of difference by Chi-Square Test.

Substitution of cholesterol for the methylprednisolone acetate in the same menstrum constituted the placebo. All patients were allowed to take any additional medication necessary for symptomatic relief, excepting for corticosteroid hormones. Seventy-eight of the ninety-five patients completed the full course of three weekly injections.

Each patient was given 2 cc (80 mgm) of depo-methylprednisolone or 2 cc of the placebo for three consecutive weeks. Since the double blind method was used, neither the physician, the nurse administering the injection, nor the patient knew which medication was given or received. A total of 450 vials were prepared, each containing 2 cc, and numbered from 1 to 150. The vials were arranged in sets of three, with all in the set having the same number. Thus, the patient always received the same numbered vial and medication: once started on either preparation, he continued with the same one throughout the study. A master list showing the assignment

SIDE REACTIONS				
Weight				
Blood Pressure				
Urinary Frequency				
Nocturia				
Heartburn				
Flatulence				
Abdominal Cramps				
Appetite Change (+ or −)				
Epigastric Distress				
Constipation				
Hyperacidity				
Nausea				
Insomnia				
Euphoria				
Headache				
Fatigue				
Libido (+ or −)				
Muscular Cramps				
Muscular Weakness				
Acneform Eruption				
Itching				
Ecchymosis				
Palpitation				
Flushing of Face				
Moonface				
Glycosuria				

Fig. 2. Side reactions.

of numbers to medications was available only to the statistician. Each patient was given a card, previously described,[3] which provided a daily record of symptoms (severe, moderate, slight, none), with the criteria clearly and simply defined on the bottom of the card (Fig. 1). During his weekly visit, the patient was asked about specific symptoms (Fig. 2) usually expected from methylprednisolone ingestion. In addition, blood pressure, weight, and the result of urinalysis for glycosuria were recorded.

The symptom card was collected at each weekly visit, and a new one for

the next week given to the patient. When he completed his course of treatment, all data referring to him were collected and punched on an IBM card.

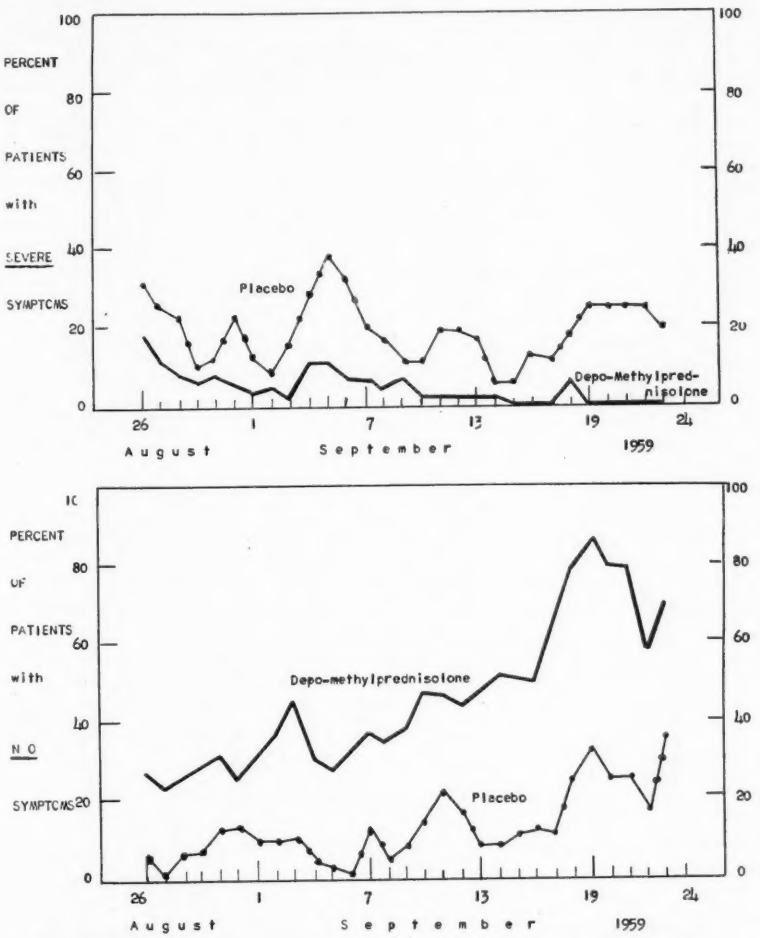


Fig. 3. Daily reported symptoms. Injection of Depo-Methylprednisolone or Placebo.

RESULTS

For the purposes of evaluation, reports of symptoms were tabluated for six-day periods (Table II). The study commenced on August 26 when the Ragweed pollen count† reached a significant level. It terminated on

†Pollen count used was tabulated daily by the Allergy Group of the Brooklyn Jewish Hospital, Brooklyn, N. Y., and published in the "World-Telegram" and "Sun" newspapers.

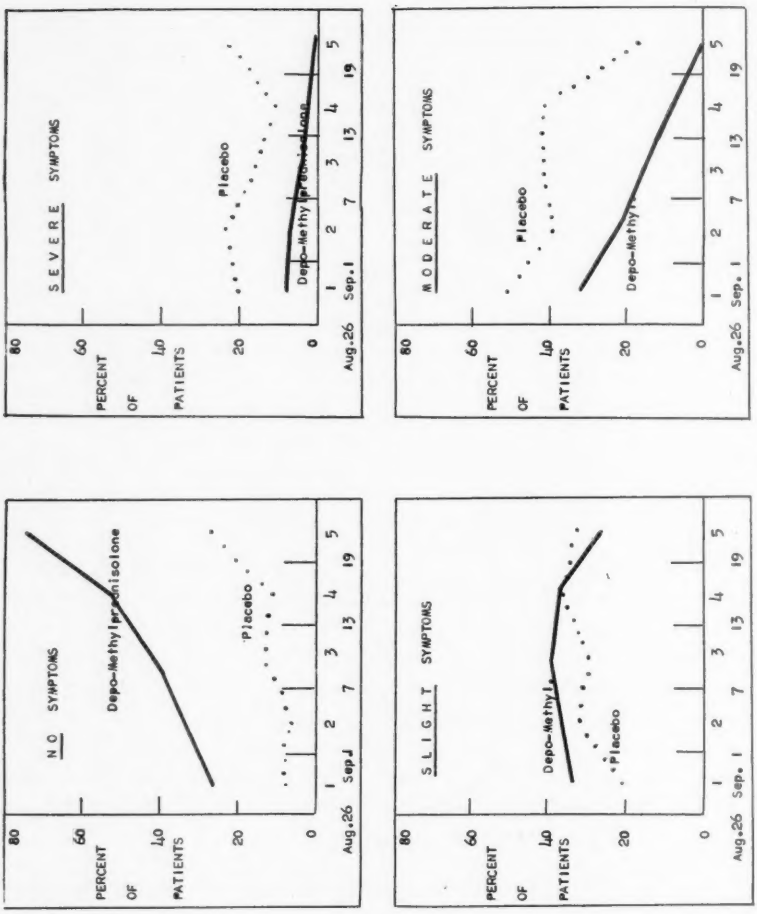


Fig. 4. Reported symptoms by calendar periods of six days' injection of Depo-Methylprednisolone or placebo.

September 18 when the amount of pollen had decreased. Patients who received the depo-steroid treatment reported a marked relief of symptoms as compared to those given the placebo. A significantly greater percentage of those patients on depo-methylprednisolone had no symptoms, and a

TABLE III. REPORTED SYMPTOMS BY FOLLOW-UP PERIODS
PATIENTS ON FULL COURSE OF THREE WEEKLY INJECTIONS
Per Cent

Symptoms	1st Injection Symptoms Reported Next 7 Days Day 1-Day 7		2nd Injection Symptoms Reported Next 7 Days Day 8-Day 14		3rd Injection Symptoms Reported Next 7 Days Day 15-Day 21	
	D-m-p	Control	D-m-p	Control	D-m-p	Control
Total trials, N—100 per cent	294	231	294	231	294	231
None	26	10	35	11	60	17
Slight	28	25	47	37	35	36
Moderate	34	42	16	33	5	36
Severe	12	23	2	19	0	10
Chi-Square probability of difference between D-m-p and control	.001 Significant		.001 Significant		.001 Significant	

significantly smaller percentage had severe symptoms as compared to those given the placebo. For instance, in the period from September 1 to September 7, the fifty patients receiving the repository steroid reported a total of 259 symptoms, while the forty-five control patients complained of 223 symptoms. Seventeen (34 per cent) of the former had no symptoms, while only three (7 per cent) complained of severe symptoms as compared to three patients (6 per cent) of the latter group who had no symptoms and eleven (23 per cent) who had severe symptoms (Table II, Figures 3 and 4).

This difference was even more marked after the second and third injections (Table III, Figure 4, No Symptoms). The patients on the steroid had increasingly less symptoms at the height of the pollen count (September 1-7) than did those of the control group. Forty-two patients had completed the three injections of repository methylprednisolone and could have had seven symptom days a week, or a total of 294 symptoms. Thirty-three patients had completed the course of the three injections of placebo and could have had a total of 231 symptoms. As the pollen season progressed and the treated patients received more medication, the steroid group became progressively more symptom-free, while the control group remained static. After the third injection, only 6 per cent of the patients on the steroid complained of severe or moderate symptoms, as compared to 46 per cent of the controls.

SIDE REACTIONS

Patients on either course of treatment had multiple reactions (Table IV). The rate of such reactions and the percentage of patients with various reactions was similar for both groups. However, a greater proportion of

patients on the placebo complained of pain at the site of injection.

A thorough search of the literature failed to elicit any symptomatology caused by cholesterol injections. The toxicity of the placebo medication has been documented previously.[5] The chief cause of complaint in this study was pain at the site of injection. Fifty-five per cent of the placebo group complained of this, compared to 20 per cent of the depo-methylprednisolone group. One patient who was later determined to have been on the depo-steroid had glycosuria. A blood sugar taken at the same time as the urine specimen showed a normal 106 mgm per cent.

DISCUSSION

Arbesman, et al,[6] and Barach, et al,[7] previously reported the effectiveness of the steroid medication in the treatment of respiratory allergies. The results we had in the treatment of ragweed hay fever with a repository steroid were equally satisfactory. This study was undertaken to determine not only the effectiveness of repository methylprednisolone, but also the incidence of side reactions following or incidental to its short term use. Skoryna, Webster, and Kahn[8] produced gastric ulcers in rats by feeding them cortisone three times a week. In examining these rats after sixty days, they found that the cortisone-treated rats had twenty-eight unhealed ulcers in 120 animals, as compared to one in 120 normal animals. Janowitz, and his co-authors[9] were able to prove that the action of cortisone directly on the gastric mucosa of dogs interfered with the healing process. However, while the healing was delayed in their experimental animals as compared to the controls, healing was definitely accomplished. These investigators concluded: "Perhaps the delay in healing of the frequently occurring asymptomatic superficial gastric ulcerations seen by gastroscopy or found in gastric specimens resected for duodenal ulcer may be the basis of these new lesions appearing in the course of corticosteroid therapy." Finally, Kammerer, Freiberger, and Rivelis[10] studied patients with rheumatoid arthritis and found that 31 per cent of 117 patients developed peptic ulcer radiographically while being treated with oral steroid medication. This compared to only 9 per cent of rheumatoid arthritic patients not receiving steroids, and 5 per cent of the non-rheumatoid controls. Because peptic ulceration is one of the most feared complications of steroid therapy, it was hoped that by using the repository steroid and thereby by-passing the gastric mucosa, such a complication might be avoided. This study, short term in nature, would in itself not adequately prove such a contention. Those studies are in progress and will be reported at a future date.

The fact that evaluation of side reactions of an active medication requires suitable controls must be emphasized. Apparently, in short-term therapy with depo-methylprednisolone, side effects are not significant. Although 239 side reactions were reported by the patients, only 14 per cent receiving methylprednisolone stopped treatment short of the full course, compared to 22 per cent of the placebo group.

TABLE IV. SIDE REACTIONS

Type of Side Reaction Grouped in System Involved	Methylprednisolone			Placebo		
	Number of Patients With Side Reactions	Total Side Reactions In Each System	Number of Side Reactions of Each Type	Number of Patients With Side Reactions	Total Side Reactions In Each System	Number of Side Reactions of Each Type
Temperature			3			3
Pain at site of injection	10	10	10	25	25	25
Genito-urinary system	11	18		10	13	
Urinary frequency			11			7
Nocturia			7			6
Gastrointestinal system	21	47		11	26	
Heartburn			8			2
Flatulence			6			3
Abdominal cramps			9			4
Appetite gain			3			1
Appetite loss			6			2
Epigastric distress			3			3
Constipation			7			5
Hyperacidity			1			
Nausea			4			4
Diarrhea						2
Nervous system	22	39		16	32	
Insomnia			9			5
Euphoria			5			3
Headache			10			11
Fatigue			10			11
Irritability			1			
Libido gain						
Libido loss						
Jittery			2			
Depressed			1			
Vertigo			1			
Faintness						2
Muscular	6	7		2	2	
Cramps			6			2
Weakness						
Pain in arms and legs			1			
Skin	4	5		2	2	
Acneform eruption			2			1
Itching			2			
Ecchymosis			1			
Hives						1
Cardiovascular	5	5		2	2	
Palpitation			2			2
Flushing of face			3			
Metabolic	2	2		1	1	
Moonface						
Glycosuria			2			1
Total	81*	133	133	72**	106	106

*Since some patients had more than one reaction, this represents the 35 patients with side reactions in the group of 50 drug-treated patients; 15 had no side reactions.

**This represents the 36 patients with side reactions in the group of 45 placebo-control patients; 9 had no side reactions.

No effort was made in this study to determine how little medication would be necessary to control symptomatology satisfactorily. Patients not included in this study were given from 40 mgm to 120 mgm of depo-methylprednisolone in a single injection to determine how long effective relief would last. Apparently 80 mgm to 120 mgm would adequately control symptoms for eight to ten days. This one injection, causing few side reactions, would tend to maintain a constant steroid blood level. The lack of fluctuation, ease of administration, and safety would make use of this preparation in acute, self-limiting, allergic syndromes superior to the oral preparation, where steroids are indicated. The physician has full control of dosage administered.

The authors wish to emphasize that they do not advocate the routine use of steroids for ragweed hay fever. The dangers of haphazard steroid ad-

ministration must always be considered, and as in the use of all potent medication, one must weigh the disadvantages of a specific medication against the good that might ensue.

SUMMARY

1. During the 1959 Ragweed hay fever season, ninety-five patients with proven ragweed pollinosis were divided into two groups: fifty were given depo-methylprednisolone, and forty-five were given a cholesterol placebo. The choice of preparation was by the double blind method.

2. Depo-methylprednisolone was shown in this study to have no more side reactions than placebo medication.

3. Depo-methylprednisolone was an effective and safe medication to administer to patients suffering from severe Ragweed pollinosis.

BIBLIOGRAPHY

1. Brown, Earl B., and Seideman, Thomas: Comparative incidence of side reactions of methyl-prednisolone and prednisolone in allergic patients. Am. Pract. & Digest Treat., 10:813, 1959.
2. West, H. F.: Medical Memoranda. Brit. M. J., No. 5153 (Oct. 10) 1959.
3. Brown, Earl B., and Seideman, Thomas: Treatment of seasonal and perennial allergic rhinitis with predisone and prednisolone. J. Allergy, 27:305, 1956.
4. Brown, Earl B., and Seideman, Thomas: Comparison of the clinical effectiveness of methyl-prednisolone (Medrol) to prednisolone (Delta-Cortef). Metabolism, 74, Part 2, 1958.
5. Wolf, S., and Pinsky, R. H.: Effects of placebo administration and occurrence of toxic reactions. J.A.M.A., 155:339, 1954.
6. Arbesman, C. E., and Ehrenreich, R. J.: Meticorten and 9 alpha fluorohydrocortisone in treatment of allergic disorders. J. Allergy, 26:189, 1955.
7. Barach, A. L., Bickerman, H. A., and Beck, G. J.: Clinical and physiological studies on use of metacortandracin in respiratory disease. I. Bronchial asthma, Dis. Chest, 27:515, 1955.
8. Skoryna, S. C., Webster, D. R., Kahn, D. S.: A new method of production of experimental gastric ulcer: The effects of hormonal factors on healing. Gastroenterology, 34:1, 1958.
9. Janowitz, H. D., Weinstein, V. A., Shaer, R. G., Cereghini, J. F., and Hollander, F.: The effect of cortisone and corticotropin on the healing of gastric ulcer. An experimental study. Gastroenterology, 34:11, 1958.
10. Kammerer, W. H., Freiberger, R. H., and Rivelis, A. L.: Peptic ulcer in rheumatoid patients on corticosteroid therapy. Arthritis and rheumatism, 1:122, 1958.

39 West 55th Street (Dr. Brown)

ALL OF US MAY LEARN

The foremost president of the Rockefeller Foundation used to ask himself regularly once a week if he would have seen the potential promise and would have been willing to support the young Pasteur when he was struggling away in his early garret laboratory. Being certain about other kinds of excellence in the early crude stages is even more difficult. But if we can bear to work alongside a man who does or says or thinks unusual things, if we can tolerate or even relish association with those who question some of our assumptions, all of us may learn something.—J. Roby Kidd, *Adult Leadership,* The Adult Education Association of the USA.

THEOPHYLLINE BLOOD LEVEL STUDIES FOLLOWING THE RECTAL ADMINISTRATION OF REDUCED DOSAGE OF THEOPHYLLINE MONOETHANOLAMINE

HOMER E. PRINCE, M.D., F.A.C.A.

Crockett, Texas

RICHARD H. JACKSON, M.D., F.A.C.A., RICHARD L. ETTER, M.D., F.A.C.A., WARREN J. RAYMER, M.D., F.A.C.A., and FERRIN B. MORELAND, Ph.D., F.A.A.C.C.

Houston, Texas

IN A FORMER COMMUNICATION, we reported the comparative clinical effectiveness of aqueous solution of theophylline monoethanolamine (Clysmathane,® Fleet) administered rectally, and theophylline ethylenediamine (aminophylline) administered orally and rectally in both aqueous and suppository form for relief of bronchial asthma.[1] Early in these studies we observed a very narrow margin between the therapeutic and toxic levels of these xanthine drugs. Because of this finding, the full strength unit of Clysmathane was not tolerated by several of our patients for whom it otherwise afforded better relief than did any of the aminophylline preparations. To investigate further therapeutic and toxic levels, particularly in respect to Clysmathane, we studied a second series with half the dosage of theophylline monoethanolamine and the superiority of this drug was clearly evident along with a greatly reduced incidence of side effects.

Ridolfo and Kohlstaedt[2] in 1959 reported clinical relief of dyspnea from emphysema, asthma, or cardiac disease in eight patients following rectal administration of 500 mg of theophylline monoethanolamine (full unit of Clysmathane). These authors found theophylline blood levels in excess of 500 mcg per cent, the level regarded by Truitt, McKusick and Krantz[3] as necessary for diuresis.

The present studies were undertaken to determine blood levels of theophylline following administration of the reduced dosage (312 mg, or 250 mg delivered dose) which we had found in most patients to be clinically effective, and singularly free of side effects. We hoped to ascertain the time for maximum blood levels, and the time significant amounts of the

---

Dr. Prince is Consultant in The Allergy Clinic and Allergy Service, Hermann Hospital, Houston, Texas; Clinical Professor of Medicine (emeritus), Baylor University College of Medicine, Houston, Texas.

Dr. Jackson is Active Staff, The Allergy Clinic, Hermann Hospital, Houston, Texas; Instructor in Medicine, Baylor University College of Medicine, Houston, Texas.

Dr. Etter is Director of The Allergy Clinic and Chief of the Allergy Service, Hermann Hospital, Houston, Texas; Clinical Instructor of Medicine, Baylor University College of Medicine, Houston, Texas.

Dr. Raymer is Active Staff, The Allergy Clinic, Hermann Hospital, Houston, Texas.

Dr. Moreland is Director of Biochemistry, Science Unlimited, Houston, Texas; Associate Professor of Biochemistry, Baylor University College of Medicine, Houston, Texas.

drug remained in the blood, for correlation with the clinical responses we had observed in our earlier studies.

METHOD

Selection of Patients.—The tests were carried out on twenty-four asthmatic patients, ranging in age from fifteen to seventy-one years, of whom sixteen were males and eight were females. These patients had

TABLE I. MEANS OF RESULTS ON TWENTY-ONE PATIENTS

Time (Hours)	0	1/4	1/2	1	2	6	9	12
Mean	0	142	325	409	390	245	136	123
Range	0	21-260	130-778	187-948	276-609	73-422	—5-239	
Range, 19/21	0	52-228	181-598	254-651	291-588	140-349	62-208	

used xanthine drugs previously for the control of their symptoms. In order to avoid misinterpretation of results, all substances likely to duplicate the spectrophotometric pattern of theophylline were omitted, including caffeine-containing beverages, chocolate, barbiturate and salicylate drugs, for forty-eight hours before the tests. All therapeutic xanthine drugs were likewise omitted for the same period.

Administration of Drug and Collection of Blood Samples.—After a pre-medication blood sample of 8 ml was drawn, the contents of one Fleet theophylline rectal unit (new dosage of Clysmathane, 312 mg) was administered either by the patients themselves or by an attendant. The measured amount of solution remaining in the plastic container was subtracted from the original 37 ml to determine the amount of drug actually administered to each patient. The amount of drug administered varied from 218 mg to 294 mg, the average being 256 mg. None of the patients lost any of the medication.

Subsequent blood samples were drawn at fifteen minutes, thirty minutes, one hour, two hours, and four hours after administration of the drug in five patients. Samples were also taken at nine and twelve hours from an additional four patients. After it was found that at twelve hours the theophylline levels were negligible, the nine-hour routine was chosen for the remaining fifteen patients.

Determination of Theophylline.—The method of Schack and Waxler[4] and Waxler and Schack[5] (as modified by Carmichael and by us) was used. Two ml of serum, acidified with 0.06 ml of 0.1 N HCl, were extracted with 25 ml of a 20:1 mixture of freshly redistilled chloroform and isopropanol. Twenty ml of this extract were then back-extracted with 5 ml of 0.1 N NaOH. The absorbance of this solution was measured at 277 mmu and 310 mmu in a Beckman DU spectrophotometer, set to zero

with N/10 NaOH. Theophylline concentration was calculated by the formula:

$$(A_{277} - 1.3A_{310})\ 5.2 \times 10^3 = \text{mcg theophylline per 100 ml serum}$$

The theophylline concentration of the premedication or zero-time sample was then subtracted from each of the others to give the rise in theophylline over the base line concentration. A sample of the drug used in the tests was used as standard.

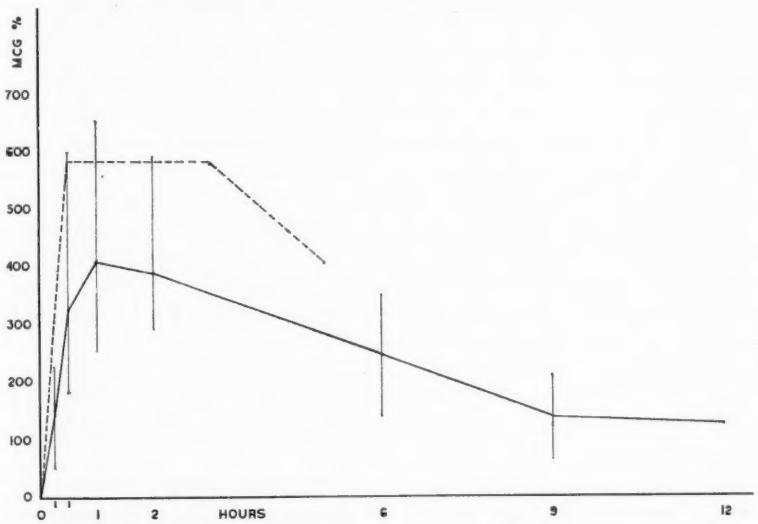


Fig. 1. Blood levels of theophylline after rectal administration of theophylline monoethanolamine. *Solid line:* serum theophylline levels from twenty-one patients herewith reported. Dose administered 250 mg. *Broken line:* plasma theophylline levels from twelve patients reported by Ridolfo and Kohlstaedt.[2] Dose administered 500 mg.

RESULTS

In three patients who had used heavy dosage of theophylline for symptomatic relief up to forty-eight hours before the tests, blood theophylline levels in the premedication samples were found high (9,050; 9,400, and 8,160 mcg per cent). Because of these high zero-time readings, further studies on the post-medication samples for these patients could not be interpreted. All these patients denied taking any theophylline or caffeine surreptitiously. We can give no explanation for the high levels in these patients, but some sort of "rebound" phenomenon seems to be a possibility.

Table I shows the means of the results on the remaining twenty-one patients (the values at twelve hours are from only four patients; these were adjusted in proportion to the mean six-hour value on these patients to that on all patients).

The range of all values is shown, also the range after eliminating the highest and the lowest values (this is approximately the 90 per cent range). (The mean of the 19/21 values was very little different from the mean of all values). These figures are more clearly shown in the graph (Fig. 1).

DISCUSSION

Our blood level determinations following administration of approximately 250 mg of theophylline monoethanolamine (the new reduced dosage of Fleet Theophylline Rectal Unit) reveal readings approximately one half those obtained by Ridolfo and Kohlstaedt[2] (Fig. 1) who employed 500 mg of the drug. Since in our earlier studies[1] we found 250 mg of this drug to be clinically effective for most asthmatic patients, with a decided lessening of side effects produced by larger amounts (500 mg), we believe the amounts of theophylline required for relief of bronchospasm are lower than previously thought necessary. It would seem that the statement of Truitt, McKusick and Krantz[3] that blood levels of 500 mcg per cent are necessary for diuresis do not necessarily apply for relief of bronchospasm. We are inclined to believe that levels of 150 to 200 mcg are effective for bronchospasmolysis. If this assumption is correct, the rapidity and duration of clinical relief observed in our earlier studies are explained by the findings herewith reported.

The persisting high theophylline blood levels at six hours after administration of the drug substantiate the cautions of other workers[6-8] concerning toxic effects of overdosage by too frequent administration of theophylline compounds.

None of the twenty-four patients in this series experienced any side effects from the dose administered. Seven patients with mild asthma at the time of the tests experienced prompt relief after administration of the drug. We could not correlate the blood levels with the amount of drug administered per pound of body weight.

Effect of Coffee-Drinking.—In order to see how much effect the drinking of coffee, before or during the test period, would have on the values obtained, we made analyses on two persons, one a heavy, the other a light coffee drinker. The heavy coffee drinker showed a concentration of 208 mcg per cent having had no coffee since the night before; a value of 198 was determined in the late afternoon after several cups of coffee. The light drinker started with a morning serum value of 57 mcg per cent which rose to 167 mcg per cent after a few cups. We wondered whether the higher readings in the heavy coffee drinker might be comparable to the unusually high readings on our three patients who had been on heavy theophylline dosage before the tests.

REFERENCES

1. Jackson, R. H., Prince, H. E., and McGivney, F.: Clinical evaluation of Clysmathane. Ann. Allergy, 18:620, 1960.

2. Ridolfo, A. S., and Kohlstaedt, K. G.: A simplified method for the rectal instillation of theophylline. Am. J. M. Sc., 237:585, 1959.
3. Truitt, E. B., McKusick, V. A., and Krantz, C., Jr.: Theophylline blood levels after oral, rectal, and intravenous administration, and correlation with diuretic action. J. Pharmacol. & Exper. Therap., 100:309, 1950.
4. Schack, J. A., and Waxler, S. H: An ultraviolet spectrophotometric method for determination of theophylline and theobromine in blood and tissues. J. Pharmacol. & Exper. Therap., 97:283, 1949.
5. Waxler, S. H., and Schack, J. A.: Administration of aminophylline (theophylline ethylenediamine). J.A.M.A., 143:736, 1950.
6. White, B. H., and Daeschner, C. W.: Aminophylline (theophylline ethylenediamine) poisoning in children. J. Pediat., 49:262, 1956.
7. Soifer, H.: Aminophylline toxicity. J. Pediat., 50:657, 1957.
8. Nolke, A. C.: Severe toxic effects from aminophylline and theophylline suppositories in children. J.A.M.A., 161:693, 1956.

P.O. Box 979, Crockett, Texas (Dr. Prince)

FOURTH INTERNATIONAL CONGRESS OF ALLERGOLOGY

The Fourth International Congress of Allergology will be held at the Hotel Commodore, New York City, from October 15 through 20, 1961. At the main meeting, papers will be simultaneously translated into English, French, German and Spanish. Prominent physicians and scientists from all parts of the world have been invited to participate in conferences, symposia and panel discussions. Some of the topics to be examined are: genetics in allergy, acquired tolerance, transplantation immunity, drug hypersensitivity, contact allergy, general mechanisms in allergy, mechanisms of antibody fixation, delayed hypersensitivity, auto-immune processes, steroid therapy and new methods in allergy.

All registered physicians are invited to present communications in the sections which correspond to their subject matter. Entertainment will include several receptions, one of which will be held at the Metropolitan Museum of Art, and a banquet. A program of luncheons, fashion shows and visits to the United Nations and other points of interest has been scheduled for the ladies.

The registration fee for regular members will be $45.00 and $20.00 for the wives. This fee includes the printed proceedings and admission to the receptions. The banquet is an extra expense. Those interested in attending the Congress should obtain additional information as soon as possible from Dr. William B. Sherman of 60 East 58th Street, New York 22, New York.

ALLERGY SESSION, AMERICAN MEDICAL ASSOCIATION

All those desiring to submit abstracts for the session in allergy of the American Medical Association in New York City in June, 1961, should forward a 250 word abstract in triplicate to Murray Dworetzky, M.D., Secretary, 115 East 61st Street, New York 21, New York.

A PROTOTYPE OF AN ASTHMATIC UNIT IN A GENERAL PEDIATRIC CONVALESCENT HOME

MARTIN GREEN, M.D. and DAVID B. ALLMAN, M.D.
Atlantic City, New Jersey

CONVALESCENCE is defined as the "gradual recovery of strength and health after a disease." This definition is the underlying philosophical concept governing the selection of appropriate patients for most pediatric convalescent homes. In practice, many convalescent homes accept two types of patients: custodial patients and convalescent patients. Custodial patients are nursing problems. They receive minimal treatment and show little or no improvement during their usually prolonged residence in an institution. To return these patients to their homes would often place an unbearable burden on their parents. On the other hand, convalescent patients under treatment in such institutions improve significantly and subsequently return to their own family units without disrupting the entire home life.

By definition, pediatric convalescent homes should accept only convalescent patients, and pediatric nursing homes should have the responsibility of the custodial children. Institutionalization of children with intractable asthma represents convalescent care at its best. Such a child leaves a family unit that has been completely disrupted by his severe asthma. On admission, he is frequently an undersized, emphysematous, wheezing child with a "hangdog" expression and the outlook of a permanently invalided patient. While in residence, this child receives active allergic and psychiatric treatment. When he is discharged he is frequently improved to such an extent that he can join his own family group without disrupting their entire home life.

The advantages of institutional care of the child with intractable asthma were recognized in 1930 by Peshkin.[1] This recognition followed observations that children with severe asthma often improve during hospitalization, although there is little change in the immediate aero-biological environment and practically no treatment of the asthma. Peshkin defined intractable asthma as severe, perennial asthma, requiring frequent hospitalization and not responding to the accepted standards of allergy practiced in the child's own community. Ten per cent of all asthmatic children fall in this group. Tufts[2] has estimated that there are well over 200,000 such cases.

Approximately 350 institutional beds are available in the United States

From the Pediatric Department, Jefferson Medical College, Philadelphia, Pennsylvania and the Betty Bacharach Home, Longport-Atlantic City, New Jersey.

Dr. Green is Associate in Pediatrics, Jefferson Medical College; Pediatric Allergist, Betty Bacharach Home, and Chief of Pediatrics, Atlantic City Hospital.

Dr. Allman is Medical Director, Betty Bacharach Home.

Presented at the Sixteenth Annual Congress of The American College of Allergists, Miami Beach, Florida, March 3, 1960.

for children with intractable asthma. The largest institution is the Jewish National Home for Asthmatic Children in Denver, Colorado. In addition, there are smaller institutions in Denver; Tujunga, California; Tucson, Arizona; Palo Alto, California, and Cincinnati, Ohio. Because of the one-year to two-year period of convalescent care for these asthmatic children, less than 10 per cent of the applicants can be admitted. The need for additional convalescent beds for asthmatic children is obvious. Rogers,[3] at a recent meeting of The American College of Allergists, suggested that convalescent homes used for patients with tuberculosis be converted to institutions for the treatment of children with intractable asthma. The staff of the Betty Bacharach Home, recognizing the need for this type of convalescent bed, recommended to the Board of Governors that an asthmatic unit be organized.

The Betty Bacharach Home is located in Longport, at the southernmost tip of Absecon Island. Steen[4] states that climato-therapy is important in the treatment of intractable asthma, but Unger[5] disagrees. Climate probably plays little role in the results achieved in the treatment of intractable asthma, but there is certainly some advantage, as noted by Gelfant,[6] in the fact that Absecon Island is a relatively pollen-free area.

This paper records our experiences in the actual process of establishing an asthmatic unit. Four basic problems had to be considered: (1) use of present physical facilities, (2) obtaining professional personnel, (3) admitting and organizing the new asthmatic children for group living and (4) methodology of diagnosis and treatment. A number of other heterogenous problems posed themselves during our initial year.

Many phases of the program depend on the available structural layout. Our program was easily planned and arranged around the excellent physical facilities of the Betty Bacharach Home. The unit was established on the third floor of the Home. This is a forty-bed ward divided into cubicles of four beds each.[7] The ward occupies the entire floor except for one private room with two beds. The asthmatic children are completely isolated from the other children in the institution. The cubicles are glassed from 3 feet above the floor. Curtains are available for the cubicles in which older children reside. Privacy is thus obtained at will, but during sleeping hours all the children can be observed from the nurses' station. One cubicle or the private room is used for illnesses necessitating isolation techniques. The ward is so constructed that the easterly exposure overlooks the ocean and the westerly exposure, Egg Harbor Bay. There are two large play rooms in the ward. Sufficient toilets, wash bowls, showers and tubs are available to satisfy the basic needs of forty children. The children are served in a large dining room. The auditorium is used as a meeting room and gymnasium. Outside athletic recreational facilities are available in a spacious yard, and a bathing beach is within 500 feet of the Home.

Our second problem was the dearth of professional personnel. Staff

physicians donate their services, and their time is often limited. Restrictions of available professional personnel, rather than the number of beds, have limited the census to twenty-three children at any one time. This is unfortunate, for despite the newness of the asthmatic unit, more than seventy completed applications have been received. The professional staff consists of a pediatric allergist, a psychiatrist, a psychiatric social worker, a psychologist, an allergy technician, a school teacher, nurses and ward attendants. One of the major factors contributing to the success of the asthmatic unit has been its affiliation with Jefferson Medical College. Representative physicians of Jefferson Medical College act as consultants, and their advice and participation in this program have been extremely advantageous. Other units placed the children under the supervision of house mothers. A number of qualified women were employed in this capacity. They were finally found unnecessary, because the nursing and attendant staff were always present, and the children selected one of these women as a mother figure.

Admitting and organizing children for group living presented our third problem. The criterion for admission, of course, is intractable asthma. Tufts[8] enhanced Peshkin's definition of intractable asthma by stating that a thorough allergy survey must have been completed, and allergy therapy must have been continued for at least one year with little or no results. Children from the ages of five to thirteen years are admitted. The previous clinical history of each child applying for admission is carefully reviewed. The intractability of the asthma is determined on the basis of the number, severity, and duration of attacks; frequency of hospitalization, extent of treatment of the allergic components, and the existence of any emotional problems. Regional consultants as defined by Peshkin,[9] have not been appointed. Such consultants presently appear unnecessary for a small asthmatic unit, if the complete clinical history is carefully reviewed before admission.

The routine of admission is simple. The parents are interviewed by the allergist and a medical history obtained. The parents are informed that all admissions are originally for a trial period of one month. During this trial period, the staff determines whether the child will cooperate in and benefit from group living. Only two children had to be sent home at the end of the trial period. The child is then examined and admitted to the asthmatic ward. The new patient is placed in a cubicle with children of similar age and of the same sex.

Two months after the first group of children were admitted, our census was fifteen. These fifteen children came from areas as far as 1,000 miles from the Home. The economic status of the parents ranged from extreme poverty to comfortably well off. The organization of this group was difficult because of the diverse cultural and familial backgrounds. In addition, one child was somewhat paranoid and kept the group in a state of unrest. After one month he was discharged, and the group was finally organized. It is

relatively simple to fit new admissions into a co-operatively adjusted group of children. The careful selection of children for admission to an asthmatic unit is an absolute necessity. They must be children who will accommodate themselves to the problems of group living.

The problem in the medical supervision of these children was keeping both diagnosis and treatment from becoming routine. The primary objective of treatment, of course, is the arrest or cure of the asthma. Every effort is made to do this in as short a time as possible. The allergist, following an admission history and physical examination, takes skin tests of each child. Skin tests for inhalants, pollens, and molds are carried out by the intradermal technique. Tests for food sensitivities are performed by the scratch and intradermal techniques and by elimination diets. All children are hyposensitized, if the history and skin tests suggest the necessity for this type of treatment. Acute attacks of asthma are treated with bronchodilators, adreno-cortical steroids when necessary, and other methods. These methods are directed at achieving the most rapid relief of the attack. Pulmonary function is determined when a child is admitted as well as a number of times during the child's residence in the institution.

The program of psychiatric therapy is a total psychotherapeutic approach with emphasis on a well-rounded routine of exercise, outdoor play, and group and individual therapy. Each child is evaluated psychiatrically on his admission to the institution. This psychiatric service is rendered by the Atlantic County Guidance Center. This entrance procedure represents an area of co-operation between two agencies supported by the general public. The parents are scheduled for an entire morning session with the psychiatric social worker. Should she deem it necessary, the parents are interviewed again or seen by the Center's psychiatrist. The child, at a subsequent appointment, is tested by the psychologist. The basic tests are the Wechsler Intelligence Scale for Children, the Blacky Pictures Test, the House-Tree-Person Test, and the Most Unpleasant Concept Test. He uses others as deemed necessary. On another day, the child is interviewed by the psychiatrist. At the conclusion of these procedures, a staff evaluation meeting is held, attended by the psychologist, psychiatrist, psychiatric social worker, school teacher and pediatric allergist. If psychiatric treatment is deemed necessary, it is undertaken by the psychologist under the guidance of the staff psychiatrist. If psychiatric guidance is necessary for the parents, arrangements are made with a psychiatrist or a psychiatric clinic located in the area of the parents' residence.

Educational facilities for the first eight grades are provided in the institution. On the basis of school records and psychological testing completed at the Home, the child is placed in the appropriate grade. The educational program is oriented toward small group teaching. The children are assigned either to a morning or afternoon school session. The teacher is a licensed New Jersey teacher with additional training in the problems of

the handicapped child. Periodic achievement tests are given to the children to measure their progress against the average child of the same age. Abnormalities such as speech and hearing defects are noted and arrangements made for their correction.

The day-to-day routine, of course, differs in the winter and summer. In the winter, the child is occupied mainly with school and homework. Outside recreational facilities are used, weather permitting. Weekends are spent in outdoor play and indoor games. All children attend religious services of their parents' designation on Sunday. In the summer, a camp routine is instituted. A head counselor and five assistant counselors supervise the group during the school vacation. Organized play and handicraft are part of the routine. Weather permitting, the children bathe in the ocean daily.

Visits by parents are permitted frequently. Visiting is limited to weekends. The parents are permitted to see their child both Saturday and Sunday afternoons. The child may be taken from the Home by the parents on these days. The specific effects of the frequent parental visits are practically nil. There appears to be little difference in the child following these visits. Such a difference would be apparent from objective signs, such as a rapid pulse rate, increased respirations and wheezing; or subjective signs, such as agitation, irritability or nightmares.

As stated previously, many heterogeneous problems arose in our first year of operation. The parents originally arrive, enthusiastic and willing to take any steps to improve the welfare of their child. They insist they will cooperate in obtaining psychiatric guidance. Fifty per cent of the parents, for one reason or another, fail to obtain this psychiatric help. This failure rate has been lessened by warning the parents of the possibility of discharging their child unless psychiatric guidance is obtained. After a period of four or five months, particularly if the child has been asthma-free, there are urgent requests from the parents that the child be permitted to come home. Such requests have been made more frequently by parents who are not receiving psychiatric help.

A number of children have been discharged in too short a period. On their return home, asthma recurred, although it was usually easily controlled. One child had to be readmitted to the institution. No child should be discharged in less than one year. All children should be properly prepared by discussions with the nurses and doctors for discharge and return to their homes.

Group discussions with the parents presented problems and finally had to be abandoned. The parents were divided into two groups to meet once monthly, and discussions were uninhibited. For the first three or four months, only constructive analysis and criticism were considered. After this, even under direct guidance, the program often degenerated into one of mild criticism of the procedures in the unit. When the allergist attended the group guidance session, he was overwhelmed by the questions relating

to each individual child. This, of course, was due to the fact that under the original organization plan, too little time had been allotted to the orientation of the parents. This has been corrected.

These children have little physical tolerance. They tire easily and need rest frequently. It is often difficult to determine their physical tolerance, and during the summer camping session they are occasionally taken beyond this point.

SUMMARY

There is an urgent need for additional beds for children with intractable asthma. The Betty Bacharach Home, a general pediatric convalescent home, recognizing this fact, established an asthmatic unit in September, 1958. In establishing this unit, certain problems were met and solved. These problems were: (1) use of the present physical facilities in establishing the unit, (2) obtaining professional personnel, (3) organizing the new asthmatic children for group living and therapy and (4) methodology of diagnosis and treatment. The method of organizing this unit and the solution of the individual problems are stated. This paper is presented as a guide for other general pediatric convalescent homes planning to establish asthmatic units.

REFERENCES

1. Peshkin, M. M.: Role of environment in the treatment of a selected group of cases of asthma. A place for a "home" as a restorative measure. A.M.A. J. Dis. Child., 39:773 (Apr.) 1930.
2. Tuft, H. S.: Report presented at the meeting of The American College of Allergists, Atlantic City, N. J., April, 1958.
3. Rogers, H. L.: Report presented at the meeting of The American College of Allergists, San Francisco, California, March, 1959.
4. Unger, L. and Johnson, J. H.: Bronchial asthma. VI. Critical review of literature. Ann. Allergy, 15:4, 5, 6 (Jul.-Aug., Sept.-Oct., Nov.-Dec.) 1957.
5. Steen, W. B.: Rehabilitation of children with intractable asthma. Ann. Allergy, 17:864-871 (Nov.-Dec.) 1959.
6. Gelfant, H. H.: Botany and allergy, New York J. Med., 58:227 (Jan. 15) 1958.
7. Bernstein, L., Kreindler L., Ghory, J. E., Fragge, R. G., Gueron, M.: Pulmonary function in children. II. J. Allergy, 30:541 (Nov.-Dec.) 1959.
8. Tuft, H. S.: The development and management of intractable asthma in childhood. A.M.A. J. Dis. Child., 93.251 (Mar.) 1957.
9. Peshkin, M. M.: Management of the institutionalized child with intractable asthma. Ann. Allergy, 18:25 (Jan.) 1960.

1922 Pacific Avenue (Dr. Green)

TRUE EDUCATION

A person truly educated in the humane tradition should have an orderly and disciplined mind—so far as any system of training can bring order into private personality. He has been taught the relationship between cause and effect. He shall understand that predictable consequences follow from particular actions. He has in his mind a fund of precedent. He is acquainted with system. He has been taught respect for just authority, and that the ego must be kept in check.—RUSSELL KIRK, "The Inhumane Businessman," *Fortune*, May, 1957.

STUDIES OF AN ANTISEROTONIN COMPOUND (Ro 2-9102) USING MICE UTERI IN ESTRUS IN A SCHULTZ-DALE APPARATUS

JOHN P. McGOVERN, M.D., F.A.C.A., KEMAL OZKARAGOZ, M.D., ALBERT E. HENSEL, JR., M.D., and KENNETH L. BURDON, Ph.D., F.Sc.

Houston, Texas

DURING the past several years the importance of 5-hydroxytryptamine (serotonin or 5-HT) in allergy has been well delineated.[1] Woolley[2] in 1952 first attempted to study the effectiveness of antiserotonin agents in laboratory animals. Since then a number of serotonin antagonists of varying chemical structure, such as yohimbine and ergot alkaloids,[3,4] chlorpromazine,[5] promethazine,[6] nicotinamide[7] and the benzyl analogs of bufotenin and serotonin[8] have been studied. In more recent work diethylamide lysergic acid has been demonstrated to be an active antagonist of 5-HT.[6,9,10]

Various whole animals and isolated tissues have been used to assay these antagonists of 5-HT by such methods as perfusion techniques,[4,8,11] artery ring methods,[3] abolition of toxic effects of 5-HT in whole animals[6,12-15] and Schultz-Dale reactions.[5,7,10,16,17] The animal most frequently used for studies of this latter type has been the rat. Erspamer[18] found the rat's uterus in estrus to be very sensitive to 5-HT when tested in the Schultz-Dale apparatus, but the uteri from rats in diestrus were relatively insensitive. We have found that this difference in sensitivity of the uterine tissue from animals in estrus and not in estrus is also exhibited to a marked degree in mice.[19] The much greater reactivity of the estrous mouse uterus was established by quantitative tests with small amounts of serotonin, acetylcholine, and specific antigen, using the sensitive electronic recording device called the physiograph[20] to record the muscle contractions.

In the present study we undertook to determine the effectiveness of the new antiserotonin compound N, N-Dimethyl-N'-benzyl-N'-benzoyl-1,3-propanediamine hydrochloride (Ro 2-9102)* in preventing the contractile response of estrous mouse uteri to 5-HT, as recorded with the physiograph. Attempts were made also to establish the mode of action and to determine an effective blocking dosage schedule for the experimental study of this compound.

MATERIALS AND METHODS

Tyrode's solution was made each day by dissolving the following ingredients: NaCl, 8 gm; $CaCl_2$, 0.05 gm; KCl, 0.2 gm; $NaHCO_3$, 0.5 gm; $MgCl_2$, 0.2 gm; NaH_2PO_4, 0.000375 gm; and glucose, 0.5 gm per liter of de-ionized distilled water. The pH was adjusted to 7.4.

From the Departments of Microbiology and Pediatrics, Baylor University College of Medicine, Houston, Texas.

*Ro 2-9102 obtained through Hoffmann-LaRoche, Inc., Nutley, N. J.

A stock solution of acetylcholine chloride** was prepared by dissolving 125.58 mg in 100 ml Tyrode's solution. This was equivalent to 100 mg of acetylcholine base. Immediately prior to use 1.0 ml was diluted to 100 ml with Tyrode's solution to give a concentration of 10 gamma acetylcholine base per ml.

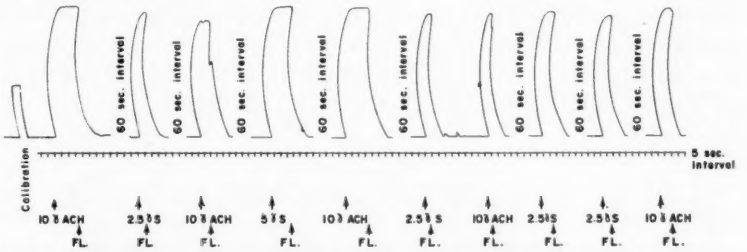


Fig. 1. Calibration=30 mm deflection; ACH=acetylcholine/20 ml Tyrode bath; FL=flush; S=serotonin/20 ml Tyrode bath. Response of uterine muscle is constant and reproducible following repeated injections of acetylcholine or serotonin at one-minute intervals.

Similarly, stock serotonin creatinine sulfate† solution was prepared by mixing 57.58 mg in 100 ml of Tyrode's solution, yielding 25 mg active serotonin base. Before use, 1.0 ml of this solution was diluted to 100 ml with Tyrode's solution to give a concentration of 2.5 gamma serotonin base per ml.

A stock solution of the serotonin antagonist was made by dissolving 100 mg (Ro 2-9102) in 10 ml of Tyrode's solution. As with other stock preparations, this was diluted immediately before use with Tyrode's solution to the appropriate concentrations to be studied. All stock solutions were stored at 4° C.

Sixty female Swiss mice weighing between 20 to 30 gm were used. The mice were put in estrus by a single intramuscular injection of 2 gamma of Estradiol§ in 0.2 ml of cottonseed oil. To be certain that estrus had been induced, vaginal smears (unstained) were studied on all animals by the method recommended by Allen.[21] Animals selected for study after vaginal smear examination were sacrificed by decapitation. Uteri were removed by midline abdominal incision and the uterine horns were separated by midsection from the cervix. These were suspended in Tyrode's solution of pH 7.4 and at 37° C and kept oxygenated with 95 per cent 0_2 and 5 per cent CO_2.

Before beginning tests the two-channel physiograph was calibrated as previously described by using a metal mass of 0.6869 gm to give a deflection of the recording needles of exactly 30 mm[19] (Figs. 1-4). Two identically constructed Schultz-Dale baths of 20 ml capacity were used. Cotton thread No. 40 was used to attach the muscle to the myograph transducer.

**Merck, Sharp and Dohme Laboratories, Rahway, New Jersey.
†Nutritional Biochemical Corp., Cleveland, Ohio.
§Depo®-Estradiol Cyclopentylpropionate, Upjohn Co., Kalamazoo, Michigan.

RESULTS

Experiment I: (Test amounts of 5-HT and acetylcholine; feasibility of repeated tests with the same uterine horn)—The amounts of 5-HT and acetylcholine necessary to produce a suitable submaximal contraction of uterine muscles, deflecting the recording needle 75 mm, were found to

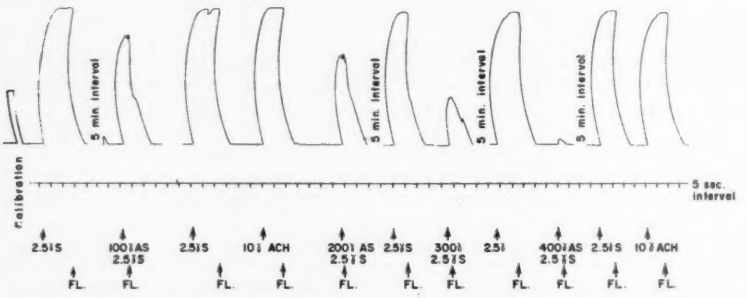


Fig. 2. Calibration=30 mm deflection; S= serotonin/20 ml Tyrode bath; FL= flush; AS= antiserotonin (Ro 2-9102)/20 ml Tyrode bath; ACH= acetylcholine/20 ml Tyrode bath. Progressive suppression of response of uterine horn to serotonin by increasing amounts of antiserotonin. (Serotonin constant; antiserotonin and serotonin mixed prior to injection into bath.)

be 2.5 gamma serotonin base and 10 gamma acetylcholine, respectively. These quantities were constant for all the individual uteri used; uteri were always from mice definitely in estrus. These test amounts of 2.5 gamma of 5-HT and 10 gamma acetylcholine were introduced repeatedly, followed by flushing each time, one after the other, into the same bath at one-minute intervals. As shown in Figure 1, this did not alter the muscle's reactivity. No tachyphylaxis under these conditions was observed during two to three hours of continual testing of a single uterine horn with this technique. The physiograph was recalibrated and baths thoroughly cleaned before repeating experiments with a new uterine horn.

TABLE I. PROGRESSIVE SUPPRESSION OF CONTRACTION OF UTERINE MUSCLE AND LENGTHENING OF MUSCLE RECOVERY TIME
(Antiserotonin increased; serotonin constant; injected following prior mixing.)

Mice	Uterine Horn	Gamma of Ro 2-9102	Gamma of 5-HT	Inhibition Partial → Complete				Muscle Recovery Time in Minutes
				+	++	+++	++++	
30	60	100	2.5	—	45	15	—	0-1
		200	2.5	—	—	45	15	1-2
		300	2.5	—	—	30	30	2-3
		400	2.5	—	—	5	55	2-4
		800	2.5	—	—	—	60	4-8

Ro 2-9102=antiserotonin
5-HT=serotonin

Experiment II: (Quantity of antiserotonin required to inhibit 2.5 gamma 5-HT after mixing the reagents in a test tube and incubating the mixtures for varying time periods)—Varying amounts of Ro 2-9102 were incubated

at 20° C in test tubes containing 2.5 gamma of 5 H-T. These mixtures were incubated from zero time to two hours before being injected into baths to determine which of the varying mixtures would produce contractions of the uterine horns.

It was found that time of incubation of the various mixtures did not alter the myographic response of the uterine tissue. Apparently, whatever reaction occurred between 5-HT and Ro 2-9102 was nearly instantaneous. Representative myographic curves resulting from tests of mixtures containing increasing amounts of Ro 2-9102 are shown in Figure 2, and the results are summarized in Table I.

Figure 2 reveals a progressively greater degree of suppression of the reactivity of the test uterine muscle with larger amounts of the antiserotonin compound in the mixtures, until in the one containing 400 gamma Ro 2-9102 the contractile effect of the serotonin is slight. In other words, when serotonin and this inhibitor are added to the tissue bath as a mixture, it is necessary to have at least 400 gamma Ro 2-9102 present to give partial suppression of the contractions usually produced by 2.5 gamma 5-HT.

The record shows further that the uterine tissue recovers within five minutes after exposure to as much as 400 gamma Ro 2-9102, mixed with 2.5 gamma 5-HT, to give normal responses to 2.5 gamma 5-HT alone, as well as to 10 gamma acetylcholine. This would indicate that this serotonin antagonist is not toxic to the smooth muscle tissue and is readily removed by washing the tissue.

Experiment III: (Relation of tissue recovery time to amount of serotonin antagonist added to the bath)—Rocha e Silva[22] suggested that the effect on an antagonist should be measured in terms of recovery time after the inhibiting substance is removed from the bath. This has been emphasized also by Fleckenstein,[23] who found that the effects of specific antagonist often lasted longer than those of less specific drugs. When experiments are limited to a single drug, recovery time increases with the dose and can be used as a measure of the action of the inhibitor. In our trials it was found, as expected, that exposure of uterine muscle to mixtures with 2.5 gamma 5-HT containing increasing amounts of Ro 2-9102 caused corresponding increases in time before uterine tissue recovered its normal reactivity. These observations are summarized in Table II and illustrated in Figure 3.

Figure 3 shows that following exposure of the uterine horn to a mixture containing 200 gamma Ro 2-9102, a time interval of approximately three minutes was required before the tissue reacted, once again, to the standard test dose of 2.5 gamma 5-HT (as previously determined); about four minutes were necessary following the test for the uterine tissue exposed to a mixture containing 400 gamma Ro 2-9102 to return to a state of reactivity; and the time element lengthened to eight minutes after a

mixture of 800 gamma Ro 2-9102 and 2.5 gamma 5-HT had been added to the bath.

These findings strengthen the impressions gained from results of the

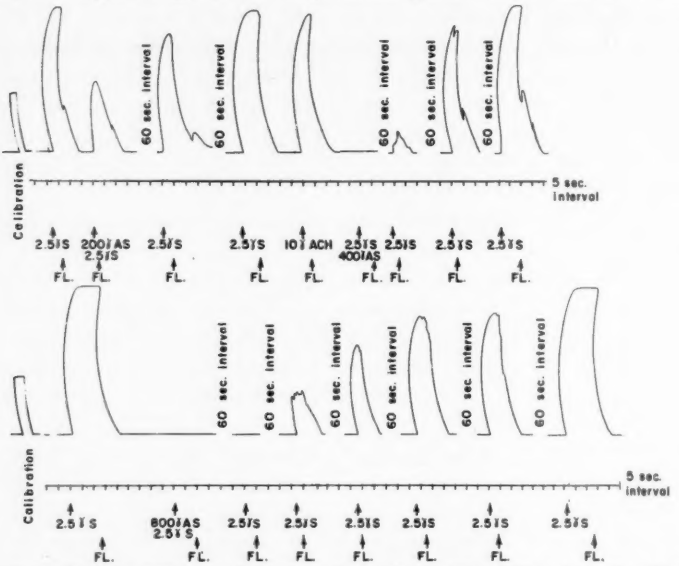


Fig. 3. Calibration=30 mm deflection; S=serotonin/20 ml Tyrode bath; FL=flush; AS=antiserotonin (Ro 2-9102)/20 ml Tyrode bath; ACH=acetylcholine/20 ml Tyrode bath. Increase of recovery time of uterine horn with increase in amounts of antiserotonin. (Serotonin constant; antiserotonin and serotonin mixed prior to injection into bath.)

previous experiment: the effect of this serotonin antagonist is upon the uterine tissue, protecting it for a period from the action of 5-HT, but not affecting the return of the tissue to its normal state of sensitivity when all the Ro 2-9102 has been washed away.

Experiment IV: (Amount of Ro 2-9102 required to inhibit the action of 2.5 gamma 5-HT when introduced first; effect of time interval before testing with serotonin) — The preceding experiment shows that large amounts of Ro 2-9102 are needed when mixed in a test tube with serotonin

TABLE II. PROGRESSIVE SUPPRESSION OF UTERINE MUSCLE CONTRACTION AND LENGTHENING OF MUSCLE RECOVERY TIME
(Antiserotonin increased; serotonin constant; antiserotonin injected before serotonin.)

Mice	Uterine Horn	Gamma of Ro 2-9102	Gamma of 5-HT	Inhibition Partial → Complete				Muscle Recovery Time in Seconds
				+	++	+++	++++	
30	60	25	2.5	15	45	—	—	15-30
		37.5	2.5	—	—	30	30	20-40
		50	2.5	—	—	10	50	40-80
		100	2.5	—	—	—	60	60-90

Ro 2-9102=antiserotonin
5-HT=serotonin

to inhibit completely the contraction of test uterine horns. However, relatively moderate amounts of the antagonist were required to protect the tissue *when added to the bath beforehand* (Table II and Fig. 4).

When 2.5 gamma 5-HT was introduced to the tissue bath five to ten seconds after the addition of 25 gamma Ro 2-9102, the contractile response of the majority of the uteri tested was reduced to about one-half the amplitude regularly seen with this amount of serotonin alone. Under the same test conditions, 50 gamma of the antagonist was necessary to

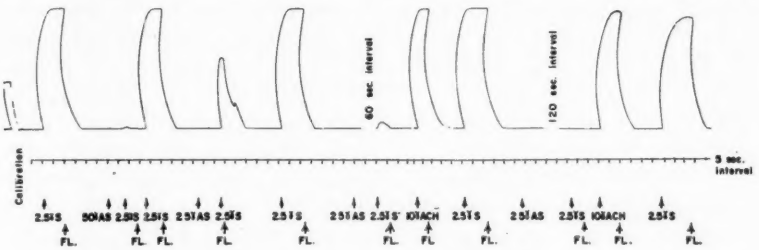


Fig. 4. Calibration=30 mm deflection; S=serotonin/20 ml Tyrode bath; FL=flush; AS=antiserotonin (Ro 2-9102)/20 ml Tyrode bath. Progressive suppression of uterine horn contraction following increase in time intervals between injection of antiserotonin and serotonin. (Serotonin constant; antiserotonin constant.)

prevent a response altogether. However, as the time interval between addition of reagents to the tissue bath was lengthened to as much as one minute, 25 gamma Ro 2-9102 was large enough to block almost completely the action of serotonin, and after a two-minute interval the addition of 5-HT produced no response. Under these conditions, as illustrated clearly in Figure 4, sensitivity of the uterine horn to acetylcholine was not diminished, showing the specificity of action of Ro 2-9102 toward serotonin.

DISCUSSION

Studies of antagonists of 5-HT with the Schultz-Dale technique have a serious drawback because of the lack of correlation between the effect of serotonin on excised tissues and on the intact animal. It is strong in the former and only slight in the latter. Nevertheless, useful information is obtained, especially when the findings can be reported on a quantitative basis, as is possible with the use of the physiograph. Contrary to other reports,[15] we have found no tachyphylaxis to "physiological" doses of 5-HT injected into bath at ten- to thirty-second intervals and thus no interference with results of necessary repeated tests with the same piece of uterine tissue. Moreover, the antagonizing effect of Ro 2-9102 was promptly removed by repeated flushing of bath. This is in contrast to the behavior of many types of serotonin antagonists whose inhibiting action is practically irreversible.

No definite mechanism of action of 5-HT has been reported in the literature, although there is evidence from the work of Rapport and

Koelle[24] that it acts directly on smooth muscle. Our findings add further support to this concept. When the antagonist was introduced first, it had an opportunity to combine with the smooth muscle before contact with serotonin. Accordingly, we found that from eight to sixteen times more serotonin antagonist was required to inhibit the action of a constant amount of 5-HT when a test-tube mixture of the two reagents was added to a tissue bath. No detectable reaction requiring the passage of time occurred when mixtures of Ro 2-9102 and 5-HT were incubated in a test tube. However, a definitely time-consuming process went on when the antagonist was added by itself to the tissue bath, and smaller amounts protected the tissue when longer periods of contact were allowed before testing with serotonin. Rapport and Koelle postulated two sites of action of 5-HT: (1) histamine site, and (2) cholinergic site. Bhattacharya[4] thinks that this hypothesis is untenable because antihistamines and atropine have no antiserotonin effect. He speculates that the action of antiserotonin compounds is based on a competitive mechanism. In our study we found increasing amounts of Ro 2-9102 necessary to inhibit correspondingly larger amounts of 5-HT. This suggests antagonism on a competitive basis as the possible mechanism of action.

Specific antagonism is commonly due to the competitive action of drugs similar in structure to the active drug. There is some evidence that some of the actions of 5-HT are due to combination with special receptors called tryptamine receptors, which are different from those of histamine, Adrenalin or acetylcholine.[25] In every experiment and with each individual uterine horn a test of specificity was carried out by comparing the effect of 5-HT with that of suitable doses of acetylcholine before and after addition of antagonist. From our tests we believe that Ro 2-9102 is a specific antagonist of 5-HT because of its ability to depress or inhibit responses to 2.5 gamma of 5-HT while not changing the responses to 10 gamma of acetylcholine. We are aware that this does not prove that 5-HT and Ro 2-9102 are competing for the same receptor site.

SUMMARY

1. A new antiserotonin agent, Ro 2-9102, was studied using mice uteri in estrus in a Schultz-Dale apparatus, with quantitative records provided by the physiograph.

2. Ro 2-9102 showed specific antiserotonin activity by this technique and merits further study.

3. This antagonist was shown to exert its protective effect by prior contact with the smooth muscle tissue and not by direct reaction with serotonin itself. It is postulated that the drug probably competes with 5-HT for a common receptor site on the smooth muscle. Unlike many other antiserotonin compounds, Ro 2-9102 does not poison the tissue, since normal reactivity returns promptly when the drug is washed away.

4. The uteri of mice in estrus were found to be well suited for studies of this type.

REFERENCES

1. Page, Irvine H.: Serotonin (5-hydroxytryptamine); the last four years. Physiol. Rev., 38:277, 1958.
2. Woolley D. W., and Shaw, E.: Some antimetabolites of serotonin and their possible application to the treatment of hypertension. J. Am. Chem. Soc., 74:2948, 1952.
3. Shaw, E. and Woolley, D. W.: Yohimbine and ergot alkaloids as naturally occurring antimetabolites of serotonin. J. Biol. Chem., 203:979, 1953.
4. Bhattacharya, B. K.: A pharmacological study on the effect of 5-hydroxytryptamine and its antagonists on the bronchial musculature. Arch. Int. Pharmacodyn., 103:357, 1955.
5. Gyermek, L., Lazar, I. and Csak, A. Z.: The antiserotonin action of chlorpromazines and some other phenothiazine derivatives. Arch. internat. pharmacodyn., 107:62, 1956.
6. Rose, J. C. and Lazaro, E. J.: Pulmonary vascular responses to serotonin and effects of certain serotonin antagonists. Circulation Res., 6:282, 1958.
7. Woolley, D. W.: Tranquilizing and antiserotonin activity of nicotinamide. Science, 128:1277, 1958.
8. Stormorken, Helge: The antiserotonin effect of the benzyl analog of bufotenin (BAB) and the benzyl analog of serotonin (BAS) in the isolated guinea pig lung. Arch. internat. pharmacodyn., 119:232, 1959.
9. Smythies, J. R.: Qualitative measurement of the effect of lysergic acid diethylamide on mice and its interactions with other drugs. Nature, 183:545, 1959.
10. Sollero, L., Page, I. H. and Salmoiraghi, G. C.: Brom-lysergic acid diethylamide: A highly potent serotonin antagonist. J. Pharmacol. & Exper. Therap., 117:10, 1956.
11. Bhattacharya, B. K. and Delaunois, A. L.: An improved method for the perfusion of isolated lung of guinea pig. Arch. internat. pharmacodyn., 101:495, 1955.
12. Woolley, D. W.: Convenient method for assay *in vivo of* antimetabolites of serotonin. Proc. Soc. Exper. Biol. & Med., 98:367, 1958.
13. Slaytor, M., Pennefather, J. N. and Wright, S. E.: Metabolites of L. S. D. and ergotmetrine. Experentia, 15:111, 1959.
14. Shaw, E. and Woolley, D. W.: Benzylmethylbufotenin, a powerful antimetabolite of serotonin. Proc. Soc. Exper. Biol. & Med., 93:217, 1956.
15. Shaw, E. and Woolley, D. W.: Methylserotonins as potent antimetabolites of serotonin active both *in vitro* and *in vivo*. J. Pharmacol. & Exper. Therap., 116:164, 1956.
16. Brittain, R. T. and Collier, H. O. J.: Antagonism of 5-hydroxytryptamine by dock leaf extracts. J. Physiol., 135:58P., 1957.
17. Gaddum, J. H. and Hameed, K. A.: Drugs which antagonize 5-hydroxytryptamine. Brit. J. Pharmacol., 9:240, 1954.
18. Erspamer, V.: Enteramina e 5-metossitriptamine: Tossicita; azione sulla diuresi, sulla pressione del sangue e su alcuni organi a muscolatura liscia. Ricerca Scient. e Ricostruz, 22:694, 1952.
19. Burdon, K. L., Ozkaragoz, K., Kaufman, H. S. and McGovern, J. P.: The effect of estrus on the response of the excised mouse uterus to serotonin, acetylcholine, and specific antigen: Schultz-Dale tests with the physiograph. Ann. Allergy, 18:972, 1960.
20. Hoff, H. E., Geddes, L. A. and Spencer, W. A.: The Physiograph—an instrument in teaching physiology. J. Med. Educ., 32:181, 1957.
21. Allen, E.: The oestrous cycle in the mouse. Am. J. Anat., 30:297, 1922.
22. Silva, M. Rocha e: The mechanism of recovery of the guinea pig gut from inhibition by atropine and antihistaminics. Exper. Med. & Surg., 8:346, 1950.
23. Fleckenstein, A.: A quantitative study of antagonists of Adrenaline on the vessels of the rabbit's ear. Brit. J. Pharmacol., 7:553, 1952.
24. Rapport, M. M. and Koelle, G. B.: The action of antihistaminics and atropine in blocking the spasmogenic activity of serotonin on the guinea pig ileum. Arch. Internat. Pharmacodyn., 92:464, 1952.
25. Gaddum, J. H.: Tryptamine receptors. J. Physiol., 119:363, 1953.

HYDROALCOHOLIC THEOPHYLLINE PREPARATION (ELIXOPHYLLIN®) IN THE MANAGEMENT OF BRONCHIAL ASTHMA

A Three-Year Study Giving a Comparison with the Widely Used Anti-Asthmatic Drugs

ELY PERLMAN, M.D., F.A.C.A.
New York, New York

THE XANTHINE DRUG, theophylline, combined with ethylenediamine (aminophylline) has been one of the most useful drugs for the symptomatic relief of bronchial asthma. Its long and continued use is indicative of its value. Although aminophylline has been administered orally, rectally, intramuscularly and intravenously, its bronchodilating effect is most striking by the intravenous route.

The oral use of the medication in effective doses, 200 to 300 mg t.i.d. or q.i.d., has been somewhat restricted because of gastric intolerance. To avoid this gastric distress, the drug has been combined with aluminum hydroxide or has been given as an enteric-coated tablet. Since aminophylline in tablet form is rather slowly absorbed, these measures, while occasionally helpful, retard absorption and further delay the onset of action.

The xanthine salt also has been extensively employed as a rectal suppository, especially in infants and children, but Waxler and Schack[1] have shown that absorption by this method is erratic and undependable. In some individuals, blood theophylline levels were exceedingly low until the fifth and sixth hours, and in others, very high levels were seen in four hours. Accordingly, "unpredictable absorption coupled with repeated administration can lead to dangerous cumulative effects with serious toxicity particularly in infants and young children."[2] Systemic reactions and even death have been reported by Nolke,[3] Rounds,[4] Love and Corrado[5] and others.

In order to increase its anti-asthmatic action, theophylline has been administered together with ephedrine. The combination of 130 mg of theophylline, 25 mg of ephedrine sulfate and 8 mg of phenobarbital undoubtedly has been one of the most widely used symptomatic medications employed for the control of chronic asthma.

A solution of free theophylline* became available approximately four years ago. At that time, reports of preliminary clinical trials indicated that this oral liquid medication was of value in the management of coronary disease[6] and asthma,[7] and its continued use was accompanied by a low inci-

---

From the Allergy Department, Department of Pediatrics and Medicine, Long Island Jewish Hospital.

*Elixophyllin®-Sherman Laboratories, Detroit, Michigan, a hydroalcoholic solution of theophylline containing 80 mg of the free base in each tablespoon of the vehicle which is 20 per cent alcohol.

dence of side effects. The clinical response was apparently due to the rapid achievement of high blood levels as judged by chemical assay.[8]

In order to determine the usefulness of this form of theophylline in the treatment of asthma and to compare this drug with other standard antiasthmatic products, an initial, controlled short-term study was instituted. In view of the encouraging results, a second study was undertaken which was extended over a three-year period.

During the course of these studies, a number of papers have appeared and presented objective as well as subjective evidence of the value of Elixophyllin® in acute and chronic asthma. Schluger, McGinn and Hennessy[9] reported that a single oral dose of 5 tablespoonfuls of Elixophyllin (equivalent to 500 mgm of aminophylline) induced higher theophylline blood levels at fifteen and thirty minutes than noted with 250 mgm[1] and 300 mgm[10] of aminophylline administered intravenously. Oscharoff[11] found higher levels during different times of the day after the administration of 2 or 3 tablespoonfuls of the liquid medication given three times daily for seven days, than after equivalent amounts of aminophylline administered at the same times.

Pulmonary function tests were performed by different investigators, and the improvements noted seemed to parallel high blood levels of theophylline. In a total of eighty-nine patients suffering an acute asthmatic attack, four or five tablespoonfuls of the preparation increased vital capacity an average of 30 per cent at thirty minutes (Spielman,[12] MacLaren,[13,14] Frank[15] and Bickerman, Pons and Barach[16]). Bickerman, Pons and Barach also reported that a single large dose of Elixophyllin is useful in enhancing the cough reflex in patients with chronic pulmonary diseases who suffer from impaired bronchial drainage. Average gains of 33 per cent in the air flow rate and over 100 per cent in volume of air expelled on maximal cough were observed by these investigators.[16]

Comparative vital capacity measurements with the use of Elixophyllin, alcohol control and theophylline control preparations were performed by Spielman[12] on patients having acute asthmatic attacks. Neither the alcohol control nor the theophylline control were of value in increasing vital capacity to any appreciable extent within thirty minutes, whereas the solution of free base resulted in a significant increase within this period of time. These results suggest that alcohol is required to hasten the absorption of theophylline.

A total of 107 patients suffering *acute* asthmatic attacks, fifty of whom were hospital emergency cases, were treated by Schluger, McGinn and Burbank,[17] Spielman,[2] Greenbaum[18] and Kessler.[19,20] Complete relief within thirty minutes was secured in eighty-five, incomplete relief in eleven, and no response in another eleven patients.

The liquid preparation was also studied to determine its effectiveness in the treatment of *chronic* asthma and bronchospastic pulmonary emphysema. Bickerman, Pons and Barach[16] treated 149 patients with three tablespoonfuls

of Elixophyllin upon arising and four tablespoonfuls at night time over a prolonged period of time. Excellent response occurred in ninety, good in thirty-six and slight or none in twenty-three. Spielman,[2] MacLaren,[13,14] Turek,[21] Kessler[19,20] and Greenbaum[18] reported good or excellent improvement in 158 of a total of 190 patients with chronic asthma treated with 2 tablespoonfuls of Elixophyllin t.i.d. or q.i.d. In a group of forty-four patients with intractable asthma, Elixophyllin was of benefit in approximately one-half of the cases (twenty-two).

METHOD AND MATERIALS

Short-Term Study.—The drug was first studied in sixty-nine children and adult patients with asthma whose ages ranged from one to sixty-nine years. They were selected at random from the Allergy Clinic, Long Island Jewish Hospital, and from private practice.

Five different treatments were alternately used on each member of this series. Some patients were started with the alcohol theophyllin solution (El), others with a tablet containing ephedrine sulfate grs ⅜ and phenobarbital grs ¼ (EP); still others with a placebo tablet (Pl) identical in appearance with the EP tablet; a fourth group with both El plus EP; and the remainder with both El and Pl.

All patients were instructed to take their medications before meals and before retiring. Patients kept a record of frequency and severity of symptoms on specially prepared score cards which were reviewed and summarized at each weekly visit. After an interval of time sufficient to determine the effect of the medication taken in optimal dose, the patient was systematically given each of the other drugs or combinations described above.

The long-term study was undertaken to determine the preference of these patients over a long period of time for each of the anti-asthmatic medications. This was based upon efficacy as well as freedom from undesirable side effects. A total of eighty-nine patients were followed for periods of one and one-half to three years. The group consisted of forty male and forty-nine female patients ranging in age from seven months to seventy-three years, including thirty-nine infants and children.

All the subjects had already tried one or another of a variety of anti-asthmatic medications. All but four of the subjects were given at least two or three of the following preparations and all were given theophylline-alcohol (El).

I	El,	Theophylline-alcohol 80 mg free base per tablespoon (Elixophyllin)
II	TEP	Theophylline 130 mg, Ephedrine 25 mg, phenobarb 8 mg per tablet (Tedral and others)
III	Elix. AD	Aminophylline 50 mg and diphenhydramine 12.5 mg per teaspoon (Elixir Hydrillin)
IV	A	Aminophylline 100 mg per uncoated Tablet
V	DAR	Aminophylline 150 mg, racephedrine 25 mg and diphenhydramine 37.5 (Hyadrine)
VI	EP	Ephedrine 25 mg and phenobarb 16 mg per tablet

All of the eighty-nine patients received El, fifty received TEB, thirty-one Elixir AD, twenty-two DAR and seventeen EP. All individuals received the medications consecutively with each exacerbation and were then allowed to continue with the product, which, in their own opinion, proved more

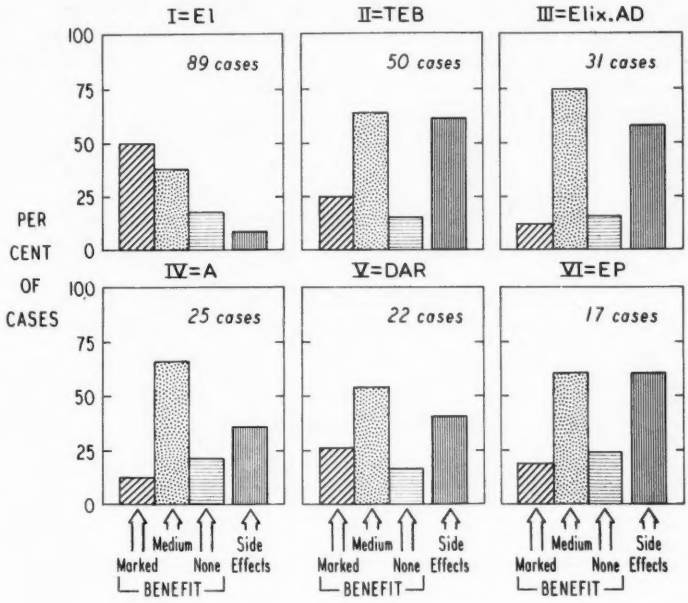


Fig. 1. Symptomatic response to anti-asthmatic medications.

I = El	—Theophylline-alcohol
II = TEP	—Theophylline, ephedrine, phenobarbital
III = Elix. AD	—Aminophylline, diphenhydramine elixir
IV = A	—Aminophylline
V = DAR	—Aminophylline, racephedrine, diphenhydramine
VI = EP	—Ephedrine, phenobarbital

acceptable and gave better results. They were additionally instructed to take 1, 2, 3, or 4 tablespoonfuls of the liquid preparation depending upon their individual tolerance and needs. Doses of other products were prescribed as recommended but the subsequent doses were adjusted in the same manner.

RESULTS

Short-Term Study.—Theophylline-alcohol (El) was well tolerated in doses of 1 to two tablespoonfuls three or four times daily. Good or excellent clinical response occurred in about 80 per cent of the patients at the higher dosage level. When given in doses of 4 or 5 tablespoonfuls at one time, it was useful in quickly curtailing acute asthmatic attacks. Four of

the sixty-nine patients complained of mild to moderate gastrointestinal distress, and a small percentage of the children disliked the taste of the preparation.

A relatively large number of the patients receiving Ephedrine-phenobarb

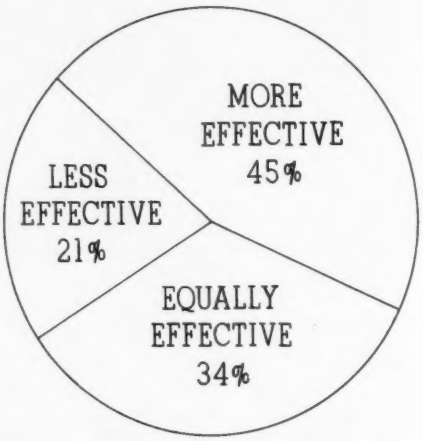


Fig. 2. Efficacy of Theophylline-alcohol as compared with other anti-asthmatic preparations tested.

(EP) complained of central nervous system effects when the dose was increased from 1 to 2 tablets t.i.d. The increase was made in order to achieve more satisfactory control of symptoms. The placebo tablet (Pl) proved of value in a few cases for a short period of time only. The group which received Theophylline-alcohol plus Ephedrine-phenobarb (El + EP) secured no greater benefits than when El was used alone. It was possible to reduce amounts of both medications, but it was quite evident that the addition of EP was responsible for some increase in side effects. The administration of Elixophyllin with the placebo gave results which were rather similar to those achieved with El alone.

Long-Term Study.—The results are summarized in Figure 1. Some degree of improvement was noted in about 80 per cent of the patients treated, regardless of the preparation used. Theophylline-alcohol (El) however, elicited more satisfactory response in a higher percentage of cases. Fifty-one per cent secured marked relief after El, 24 per cent after TEB, 10 per cent after Elixir AD, 12 per cent after A, 27 per cent after DAR, and 18 per cent after EP.

Of the seventy-six patients who had had an opportunity to receive two or more drugs, theophylline alcohol preparation (El) proved more effective in 44 per cent of the cases. In approximately 34 per cent, it was as bene-

ficial as the most effective of the five test preparations; and in the remainder some one or more of the other medicaments elicited greater response. These results are summarized in Figure 2.

Of the total number of patients treated, forty-five preferred theophylline-alcohol (El) and continued to use it exclusively (Table I). Another fourteen patients took El in combination with other medication, while the remaining thirty discontinued its use. Twenty of the thirty patients switched to other drugs in the study and found them more satisfactory. Another six patients tried other medications but secured no relief, while four did not receive any other test preparation.

TABLE I. PATIENTS' DRUG PREFERENCE OVER PROLONGED PERIOD OF TIME

A.	Number of Patients Maintained on Theophylline-alcohol Alone	45
	1. Number of these patients who had been treated with other drugs	37
	2. Number of these patients who had not received other drugs	8
B.	Number of Patients Maintained on Theophylline-alcohol in Combination With Other Drugs	14
C.	Number of Patients Who Did Not Remain On Elixophyllin	30
	1. Number of these patients who preferred and remained on other drugs	20
	2. Number of these patients who were satisfied with none of the other drugs	6
	3. Number of these patients who had not received other drugs	4

Side effects were minimal after treatment with 1, 2 or 3 tablespoons of theophylline alcohol there times a day. Two patients complained of nausea, and three of nausea and vomiting. Of the fifty patients who had received 1 or 2 tablets of TEB, t.i.d., thirty-two were disturbed by nausea, nervousness and wakefulness; and vomiting was the chief complaint in three. Undesirable effects also occurred in fifteen who had received Elixir AD, in nine who took A, in ten after DAR and in ten after EP. Drowsiness and nausea were the common symptoms following Elixir AD; nausea and heartburn after A; nausea and wakefulness after DAR; and nausea, nervousness and wakefulness after EP (Fig. 2).

DISCUSSION

Theophylline, alone or in combination with ephedrine, is without doubt the most widely used oral medicament for the control or prevention of symptoms of asthma. That both are excellent bronchodilators is unquestioned, and yet, many patients receiving oral tablets containing these ingredients find them unsatisfactory.

The explanation may be found in the difficulty in establishing a dose for each drug which will secure a therapeutic response and at the same time minimize the occurrence of undesirable local and systemic effects. To produce a therapeutic response with uncoated tablets of aminophylline, 200 to 300 mgms have to be administered three or four times daily and with lower doses, satisfactory results are rarely or less frequently attained. Severe gastrointestinal irritation, however, is frequently seen after the adminis-

tration of the 300 or 200 mgm doses and occasionally following 100 mg dose.

This paradoxical situation also applies to ephedrine. To secure a satisfactory result with this sympathomimetic, about 35 to 50 mgms has to be given three times daily. Central nervous system over-stimulation, however, results with this dosage schedule. To minimize the side effects significantly, the dose is reduced to 25 mg or less. The antiasthmatic action, however, is similarly reduced.

In the attempt to use ephedrine most advantageously, the amount in each tablet is reduced. Theophylline is incorporated to increase the bronchodilating effect, and phenobarbital is added to counteract the overstimulating effect of the ephedrine. The rationale appears fairly sound. The administration of 1 tablet t.i.d. gives somewhat better results, but full effectiveness generally required 2 tablets. Thus, gastrointestinal as well as central nervous system disturbances are further increased in incidence. The gastrointestinal effects occurring with the higher dose may be ascribed to the 240 mgms of theophylline (equivalent to 300 mgms of aminophylline), and the central nervous system effects to the 50 mgms of ephedrine.

Such interplay between dosage, response and tolerance has been observed during the course of the short-term and long-term studies. The xanthine alone, or combined with ephedrine, proved ineffective in tolerated doses and conversely gave rise in many instances to intolerance when administered in doses sufficient to procure a good response.

It is of interest that the theophylline, (in amounts equivalent to 200 mgms and 300 mgms of aminophylline) when given in alcoholic solution (El), provided good results in the majority of patients with a minimum of side reactions. The patients noted this superiority and preferred to be maintained on the solution containing the theophylline rather than on the tablets of aminophylline or theophylline in combination with ephedrine.

These unexpected attributes of the alcohol-theophylline preparation may be ascribed both to the presence of the theophylline in a free and solubilized state, which makes it more readily available for absorption from the gastrointestinal tract, and to the action of the alcohol which increases the absorption rate.[12] Moreover, the local irritation which may occur with the tablet form of the xanthine is probably decreased by the dilution factor.

For older patients with possible or definite cardiovascular problems, this alcoholic xanthine solution is the most satisfactory and safe. While it has been stated that aminophylline is not a good coronary dilator and increases cardiac output and cardiac work[23,24] recent evidence shows that both intravenous aminophylline and the alcoholic theophylline solution have definitely beneficial effects on the coronary circulation[25] due to the higher resulting blood levels. In any case, theophylline and its derivatives still remain the choice drugs for treatment of asthma in cardiac patients.

SUMMARY AND CONCLUSIONS

1. The usefulness of the new hydroalcoholic solution of theophylline (Elixophyllin) for the symptomatic relief of bronchial asthma was determined in 158 patients. In a preliminary evaluation, sixty-nine were treated with Elixophyllin, and at alternate times, with other widely used antiasthmatic drugs and their combinations. During the course of the three-year study, Elixophyllin was administered to eighty-nine asthmatic patients, and in seventy-six, the other drugs or combinations were given alternately for purposes of comparison.

2. Following the administration of the hydroalcoholic solution of theophylline, marked and moderate response occurred in about 50 per cent and 30 per cent of the patients, respectively, and equivocal or no response in the remainder. Gastrointestinal effects occurred infrequently.

3. Of the seventy-six treated with Elixophyllin, as well as with other antiasthmatic preparations in the main study, thirty-seven found the new preparation to be the most useful of all drugs tried and continued to take it exclusively. Another fourteen preferred its use in combination with other drugs. Twenty found various other drugs more advantageous, and six secured benefits from none of the agents given.

4. There was a ten-fold decrease in incidence of undesirable effects when the patients who did not tolerate the theophylline-ephedrine-phenobarbital combination were changed to the hydroalcoholic solution of theophylline.

BIBLIOGRAPHY

1. Waxler, S. H. and Shack, J. A.: Administration of aminophylline, J.A.M.A., 143:736, 1950.
2. Spielman, A. D.: Therapeutic effectiveness of elixophyllin for the oral treatment of acute and chronic asthma. Ann. Allergy, 15:270, 1957.
3. Nolke, A. C.: Severe toxic effects from aminophylline and theophylline suppositories in children. J.A.M.A., 161:693, 1956.
4. Rounds, V. J.: Aminophylline poisoning. Pediatrics, 14:528, 1954.
5. Love, F. M., and Corrado, A. G.: Aminophylline overdosage in children; report of four cases with toxic symptoms. Am. J. Dis. Child., 89:468, 1955.
6. Oscharoff, A.: Personal communication.
7. Spielman, A. D.: Personal communication.
8. Oscharoff, A., and Hennessy, D.: Personal communication.
9. Schluger, J., McGinn, J. T., and Hennessy, D. J.: Comparative theophylline blood levels following the oral administration of three different theophylline preparations. Am. J. Med. Sc., 233:296, 1957.
10. Brodwell, E. K.: Resorption of theophylline (theophylline ethylenediamine). Acta Med. Scand., 146:123, 1953.
11. Oscharoff, A.: Therapeutic effectiveness of elixophyllin as compared with aminophylline in severe angina pectoris. New York J. Med., 57:2975, 1957.
12. Spielman, A.: Comparative effectiveness of an alcohol-water solution of theophylline (elixophyllin), alcohol-water solution, and theophylline-water solution for the oral treatment of acute bronchial asthma. J. Allergy, 30:35, 1959.
13. MacLaren, W. R.: Elixophyllin in acute and chronic asthma: Evaluation by change in symptoms and pulmonary function measurements. Ann. Allergy (In press).
14. MacLaren, W. R.: Theophylline in hydro-alcoholic solution for the treatment of acute and chronic asthma: Clinical evaluation and pulmonary function studies. Calif. Med. (In press).

15. Frank, D. E.: Spirometric evaluation of a water-soluble theophylline (Elixophyllin) in acetylcholine-induced asthma. Antibiotic Med. & Clin. Ther., 6:338-342, 1959.
16. Bickerman, H. A., Pons, E. R., and Barach, A. L.: (a) The super-heated aerosol and new bronchodilator compounds. Physiologic and therapeutic evaluation. Paper delivered at Am. Col. Chest Phys. Meeting, New York City, Nov. 11, 1958. (b) Physiologic and steroid therapy in respiratory disease. Scientific Exhibit, AMA Meeting, June, 1959.
17. Schluger, J., McGinn, J. T. and Burbank, B.: The treatment of the acute asthmatic attack with an oral alcohol-water solution of theophylline (Elixophyllin). Am. J. Med. Sc., 234:28, 1957.
18. Greenbaum, J.: Clinical evaluation of Elixophyllin and choline theophyllinate in the management of acute and chronic asthma. Ann. Allergy, 16:312, 1958.
19. Kessler, F.: Non-steroid management of bronchial asthma. Med. Times (In press).
20. Kessler, F.: Clinical experience with an oral, rapidly-acting, theophylline preparation. Conn. M. J., 21:205, 1957.
21. Turek, L. H.: Drug absorption and elimination as guide to rational therapy in bronchial asthma. Indiana M. J. (In press).
22. Slepian, S.: Use of Elixophyllin in severe chronic asthma. Clin. Med., 5:57, 1958.
23. Schmidt, Carl F.: Tr. Am. Coll. Card., 1:89, 1951.
24. Master, A. M., Jaffe, H. L. and Dack, S.: The drug treatment of angina pectoris due to coronary artery disease. Am. J. Med. Sci., 197:774, 1939.
25. Russek, H. I.: Are the xanthines effective in angina pectoris? Am. J. Med. Sci., 239:109, 1960.

1176 Fifth Avenue-99th Street

THE LIBERALLY EDUCATED MAN

The liberally educated man is articulate, both in speech and in writing. He has a feel for language, a respect for clarity and directness of expression and a knowledge of some language other than his own. He is at home in the world of quantity, number and measurement. He thinks rationally, logically, objectively, and knows the difference between fact and opinion. When the occasion demands, however, this thought is imaginative, sensitive to form and affected by beauty. His mind is flexible and adaptable, curious and independent. He knows a good deal about the world culture of which he is a part, but he is never merely "well-informed." He can use what he knows, with judgment and discrimination. He thinks of his business or profession, his family life, and his avocations as parts of a large whole, parts of a purpose which he has made his own. Whether making a professional or a personal decision, he acts with maturity, balance, and perspective, which comes ultimately from his knowledge of other persons, other problems, other times and places.

He has convictions which are reasoned, although he cannot always prove them. He is tolerant about the beliefs of others because he respects sincerity and is not afraid of ideas. He has values, and can communicate them to others not only by word but by example. His personal standards are high; nothing short of excellence will satisfy him. But service to his society or to his God, not personal satisfactions alone, is the purpose of his excelling.

Above all, the liberally educated man is never a type. He is always a unique person, vivid in his distinction from other similarly educated persons, while sharing with them the traits we have mentioned.—"General Education in Schools and Colleges" from *The Bronze Mortar*, Columbia University School of Pharmacy.

Progress in Allergy

PEDIATRIC ALLERGY

A Critical Review of the Literature

SHELDON C. SIEGEL, M.D., F.A.C.A. and
BAILEY J. LOVIN, JR., M.D.
Los Angeles, California

(Continued from the November Issue)

TREATMENT OF ASTHMA

A number of excellent general papers on the management of asthma have recently been published by Levin,[131], McGovern,[132] Logan,[133] Fontana,[134] Mueller,[135] Unger *et al*,[136] Segal,[137] Krantz,[138] and Pearson.[139]

Ratner,[140] in a posthumously submitted paper, discussed some of the indications and contra-indications of the important drugs used in the treatment of asthma. He particularly emphasized the potential hazard of these drugs, especially when used indiscriminately. Some of the specific abuses pointed out were as follows: (1) The use of antihistamines for treating asthma, (2) Aminophylline administered in toxic doses to children under three years of age, (3) The use of opiates, meperidine and large doses of sedatives, (4) The routine use of oxygen, (5) The indiscriminate use of ACTH and steroids, (6) Administration of large doses of adrenalin and the use of adrenalin in oil, (7) The habit-forming effects of nebulizers. (Although the indiscriminate use of nebulizers for administering aerosols of epinephrine and related compounds certainly can lead to habituation, nevertheless, with proper instructions and warning to the parents, the reviewers believe that nebulization of these drugs can be a very useful adjunct in the management of older asthmatic children.)

Ratner's summary paragraph is worth restating: "With so many truly remarkable drugs available, we tend to accept their virtues and to overlook their dangers. I have tried to recall some of the dangers. Drugs, however valuable, must be used with discretion, not routinely. There is still no substitute for good judgment."

Sympathomimetics

Various investigations on the use of aerosols in the treatment of asthma have been reported. Reif and Mitchell[141] described several different methods of droplet-sizing for water aerosols and evaluated their relative merits. They concluded that the film method and, to a lesser extent, the methylene blue method were satisfactory for this purpose. Schiller and Lowell[142] made an appraisal of both oral and aerosolized methylphenidate hydrochloride (Ritalin®) in the management of bronchial asthma. From their studies the authors concluded that Ritalin® was relatively ineffective by either the oral or aerosolized route in the management of bronchial asthma. Zohman

and Williams[143] measured pulmonary function in several patients before and after the administration of a placebo and a new form of isoproterenol aerosol (Medihaler-Iso®). Isoproterenol administered by this method was found to have a bronchodilator effect which was independent of the alcohol-containing dispersing vehicle. Further studies led the authors to conclude that there was no significant advantage in the administration of bronchodilators with intermittent positive pressure breathing over the proper use of a hand nebulizer. Beck,[144] as well as Goldstein *et al*,[145] also concluded from their investigations that freon-propelled nebulizing preparations were a safe and convenient method of administering epinephrine and related compounds in the therapy of asthma.

Several groups of investigators, based on controlled clinical and pulmonary function studies, have concluded that Caytine® is a useful preparation that should be included in the armamentarium of the bronchodilator drugs.[146-148]

Christensen *et al*[149] reviewed the pharmacologic and therapeutic effects of ethylnorepinephrine (Bronkephrine®). The authors pointed out that clinical studies have shown that ethylnorepinephrine is an effective bronchodilator which brings relief of asthma in most patients while producing fewer side effects than those usually observed with similar doses of epinephrine. It may also be given intravenously if administered in one-fourth to one-half the usual dose over a period of seven to ten minutes. (The reviewers have used this preparation in infants and children with good results. The dose administered to children is approximately twice that of epinephrine.)

Dornhorst and Herxheimer[150] compared the circulatory and respiratory activities of d- and l-isoprenaline and concluded that although l-isoprenaline was more potent, it has no material advantage over the racemic form.

Theophylline

A number of favorable reports on the use of theophylline compounds in asthma have been published. Tuft[151] outlined his experiences with choline theophyllinate (Choledyl®) which was administered to eighty chronic asthmatic children in a dose of one tablet (200 mg) four times daily for a period of four to six weeks. He observed no side effects, and the wheezing and coughing disappeared completely in 60 per cent of the children while on the medication. Pengelly[152] found no difference in either the results or side effects when oral theophylline sodium glycinate was compared to oral aminophylline. Cass[153] observed that of forty-three adult asthmatic patients given theophylline with diethylenediamine as the solubilizing agent, eighteen patients obtained complete relief, ten moderate relief, nine slight improvement, and seven experienced no relief.

A hydro-alcohol-theophylline mixture (Elixophyllin®) containing 20 per cent ethanol and 80 mg theophylline per 15 cc has received considerable attention in the past two years. Several authors have reported favorable results with this drug in the treatment of bronchial asthma in adults.[154-157] [With reference to the pediatric age group, a preliminary evaluation of a study in progress by the authors (unpublished) reveals that Elixophyllin's active component, theophylline, is readily absorbed as indicated by determinations of theophylline plasma levels. The peak theophylline blood levels from Elixophyllin® occur at two hours, as compared to peak levels at fifteen minutes (or immediately) from intravenous aminophylline. Elixophyllin's effectiveness (in a dose of 3 mg/lb body weight) in the relief of an acute asthmatic attack appears to be equal to that of intrave-

nous aminophylline (when evaluated in a single dose study). Nevertheless, the authors were unable to determine a consistent therapeutically effective theophylline blood level in children nor was there a constant dose-theophylline blood level relationship.]

Reports[158-161] of severe aminophylline toxicities in children, resulting primarily from the abuse of the rectal suppository, continue to appear in the literature. These disturbing observations of toxicity should serve as a warning to the clinician that the amount and frequency of the dose administered of this useful, but potent, drug should be carefully regulated. A safe, effective aminophylline dose suggested by Cohen[158] and by Bacal *et al*[160] was 7 mg/kg body weight by rectal administration every twelve hours and 5 mg/kg body weight every six hours when given by the oral route. (Parents should be warned of the possible dangers from overuse. If early signs of toxicity such as insomnia, anorexia, restlessness, nausea and occasional vomiting appear, the drug should be immediately discontinued.) While epinephrine continues to be the drug of choice in the treatment of the acute asthmatic attack, the authors agree with Levin's[162] statement in his review article on the use of aminophylline in pediatrics that "aminophylline should be used judiciously, but should not be withheld because of the serious side reactions reported from its abuse."

Expectorants

The efficacy of expectorant drugs has always been a matter of controversy, and thus the statement is often made that their administration is more of an art than a science. In support of this contention were the findings of Forbes and Wise[163] in a study of the effects of ipecac, KI, inhalation of steam, inhalation of 5 per cent CO_2 and 95 per cent oxygen, and aerosols of Triton W.R. 1339 (Alevaire), trypsin and deoxyribonuclease on the viscosity of sputum. Nine patients were studied. Seven had chronic pulmonary tuberculosis and two chronic bronchiectasis. The results observed were quite variable, and none of the agents gave a consistent effect of lowering sputum viscosity. With iodides the authors suggested that in order to lower sputum viscosity it might be necessary to produce iodism. To quote from the authors, "it is odd that medicaments whose therapeutic value is supported by so little objective evidence continue to be so popular with both doctors and patients."

Hillis and Stein[164] also assessed the value of expectorant drugs in patients with chronic bronchitis. The subjects were given potassium iodide, ammonium chloride, ipecacuanha or a placebo in random order and blindly, and their effects on the viscosity and volume of sputum were determined. The authors concluded that no significant effects were noted in the viscosity of sputum. As regards subject-effect, confirmation was obtained as to the wide variation in the viscosity of sputum that occurs naturally in patients with chronic bronchitis. In these patients with chronic bronchitis and the doses used (10 grains of potassium iodide q.i.d.) only potassium iodide caused a significant increase in the output of sputum. (Both of the aforementioned studies dealt with subjects who had chronic infections and did not involve asthmatic patients. It would be interesting, since the sputum of these patients is quite different in character, to investigate asthmatic subjects in a similar manner. It also appears clear from these studies that potassium iodide is the only expectorant in chronic bronchitis and other chronic pulmonary infections that can be shown to exert an effect in humans.)

Fein[165] followed ninety cases of bronchial asthma in both children and

adults over a three-year period and felt that the use of a potassium iodide-containing bronchodilator drug reduced the incidence and severity of their asthma. The side effects noted in these patients were minimal.

To emphasize again the difference between ipecac fluid extract and ipecac syrup and their potential toxicity, Allport[166] reported the case of a two and one-half-year-old boy who after ingesting six 4 mg tablets of Chlor-Trimeton® inadvertently received 15 cc of ipecac fluid extract over a thirty-minute period to induce vomiting. The child's course was complicated by: (1) persistent severe vomiting and diarrhea lasting several days, (2) leukopenia and neutropenia possibly due to either ipecac or chlorpheniramine, (3) acute electrolyte and fluid problems including convulsions due to hyponatremia, (4) phlebitis secondary to 5 per cent NaCl administration, and (5) stenosing esophagitis necessitating bouginage therapy. (The reviewers in their practice have always been hesitant to use ipecac as an emetic in the treatment of asthmatic children. Since many of the children with moderately severe episodes of asthma are already vomiting or on the verge of it, and are often dehydrated, administration of ipecac in these children would only serve to aggravate an annoying symptom and to enhance the attendant electrolyte and fluid problems.)

Tranquilizers

The use of tranquilizers has been suggested by some authors as being a useful adjunct in the treatment of bronchial asthma and chronic pulmonary emphysema. Baum *et al*[167] in a study of thirty-five patients with bronchial asthma or chronic pulmonary emphysema concluded that chlorpromazine may be safely and effectively administered either singly or in combination with bronchodilator agents in the therapy of paroxysms of bronchial asthma and in the treatment of chronic pulmonary emphysema. Tuft[168] likewise studied the use of prochlorperazine in twenty-six hospitalized pediatric patients and in six out-patients all suffering from long-standing, recurrent bronchial asthma. The drug was administered in daily doses of 10 mg to 30 mg for periods ranging from four weeks to over four months. Fifty-six per cent of the patients showed marked improvement in terms of decreased frequency and severity of asthmatic attacks, control of the emotional factors and reduced need of corticosteroids. Twenty-five per cent showed some improvement, and 19 per cent were relatively unaffected by the administration of the prochlorperazine. No side effects were observed, and in no instance was the primary condition of bronchial asthma adversely affected.

On the other hand, in a controlled study of a small number of asthmatic patients Michelson and Lowell[169] found chlorpromazine to be of limited use in the treatment of bronchial asthma.

Additional papers on the use of tranquilizers in allergy will be reviewed in another section.

Antimicrobial Drugs

The prophylactic use of antimicrobial agents has periodically been recommended by various investigators for the treatment of bronchial asthma precipitated by upper respiratory infections. Grater[170] studied the effects of tetracycline in a group of twenty-five children who experienced exacerbation of their asthmatic symptoms with upper respiratory symptoms. Children ranging in age from one to twelve years who had previously undergone complete allergic studies but had failed to be controlled by specific therapy were given the drug orally in varying amounts ranging from 25 mg to 250

mg per dose. Treatment was given to each child from October through May, alternating with a month on tetracycline and a month on placebos. Grater felt that all the patients appeared to be benefited to some degree while on the medication. One hundred and thirty-four attacks of asthmatic bronchitis occurred during placebo therapy and fifty-nine during the administration of tetracycline. However, respiratory infections followed by asthma were not entirely abolished. In the improved group it was noted that the frequency and severity of attacks were diminished. Untoward reactions, consisting of diarrhea and occasional cramps and vomiting, occurred in four patients. In an uncontrolled study, Fishman[171] concluded that prophylactic sulfonamides were helpful in the prevention of asthma associated with infection.

In contrast to the aforementioned studies, Lewis-Faning and Davies[172] were unable to demonstrate any benefit from the administration of prophylactic penicillin. These authors carried out a controlled investigation of the efficacy of oral phenoxy-methyl penicillin (Calcipen V®) in reducing asthmatic attacks in affected children during the winter months. Thirty-five children received continuous doses of the drug from November 1956 to April 1958, and a similar number received a placebo. The results obtained by comparison of the two groups were measured in terms of the number of times an inhaler was used, the number of attacks of asthma—their duration and severity—, the amount of wheeziness, school absenteeism, and type of sputum produced. In regard to all of these indices, there was no apparent difference between the penicillin or placebo groups. Apart from three children who experienced nausea or vomiting, there were no side effects observed.

[Precipitation of asthma by respiratory infections, as well as the frequent occurrence of secondary infections complicating asthma, have continued to be a challenging problem. The reviewers have been reluctant to administer antimicrobial agents prophylactically to asthmatic children for several reasons: first, most well-designed controlled experiments on the use of prophylactic antimicrobial agents to prevent infections have (with the notable exception of penicillin to prevent streptococcal infections) failed to demonstrate any beneficial effect of any of the agents used[173-177]; secondly, complications from prolonged administration of these drugs—hypersensitivity reactions (which are more likely to occur in atopic individuals), emergence of resistant strains of organisms and of fungus infections—are serious potential hazards; and finally, since most respiratory infections in childhood are viral in origin and their course remains unaffected by the administration of antibiotics and chemotherapeutic drugs, it is difficult to understand the rationale of the beneficial effects of these agents unless one assumes their administration prevents the invasion of secondary organisms which presumably are the cause of the complicating difficulties.]

Miscellaneous Drugs

A number of other miscellaneous drugs have been advocated in the therapy of bronchial asthma. Dragsted and Hansen[178] treated seven patients suffering from bronchial asthma with nitrogen mustard gas and concluded that this preparation may be indicated in protracted resistant asthma, especially when more specific anti-allergic therapy had proved to be unsuccessful. Herxheimer[179] reviewed the literature on the burning of stramonium for the relief of asthma and reported the results of his investigations on the use of atropine administered locally in cigarette smoke or wet aerosols. The author concluded that these preparations increased the vital capacity and gave a

feeling of relief in most cases of mild to moderately severe asthmatic and emphysematous patients.

In Japan, Kusunoki *et al*[180] treated nine cases of chronic bronchial asthma with intravenous and oral para-aminosalicylic acid. Their results showed that the asthma disappeared in three of the patients, was favorably affected in another three patients and in three cases there was no improvement.

Dann *et al*[181] in a study of pamine bromide®, an anti-cholinergic agent administered intramuscularly in doses of 0.25 mg to thirty patients, demonstrated that this drug was a potent bronchodilator. The drug was shown to be effective orally in 60.9 per cent of forty-one asthmatic subjects. The authors concluded that further study of anti-cholinergic agents for the treatment of bronchial asthma is warranted. Frank[182] investigated (spirometrically) the therapeutic and prophylactic effects of diphemanil methylsulfate, epinephrine and two theophylline derivatives against acetylcholine-induced attacks of asthma in eighteen chronic asthmatic subjects. Diphemanil methylsulfate, aminophylline, epinephrine and hydroxypropyl theophylline, in that order of effectiveness, improved ventilatory function depressed by acetylcholine. When administered prior to acetylcholine, diphemanil methylsulfate and epinephrine, but not the theophylline derivatives, protected against a diminution of ventilatory function. The author felt that diphemanil methylsulfate and epinephrine can enhance the action of each other in restoring acetylcholine-depressed breathing capacity.

Schiller *et al*[183] described the use of color-coded tablets in the appraisal of several bronchodilator preparations. Hyadrine®, aminophylline with racephedrine, and a new drug, N-[β-(10-phenothiazinyl)-propyl] trimethylammonium benzene chloride and a placebo were administered to sixty-three asthmatic patients by two methods—both double-blind. In method I the preparations were identical in appearance, identified by number, and given to each patient in sequence. In method II they were identified by color and given to the patients together in a single bottle. The results showed that Hyadrine received the highest mean rating in relieving the manifestations of obstructive pulmonary disease, and aminophylline with racephedrine was a close second. The mean rating for the new drug was considerably lower and the placebo made the poorest showing. When the data from methods I and II were subjected to statistical analysis and compared, no significant differences in results were found. The authors concluded that the single bottle, color-coded method of appraisal provides information equivalent to that obtained by the conventional methods.

The treatment of asthma with steroids and corticotropin will be discussed under a separate section.

The use of bacterial vaccines in the treatment of asthma remains a controversial issue. Gundy[184] reported favorable effects from the use of acellular bacterial antigen complex (Hoffmann) and administered it to twenty-five children ranging in age from two and one-half to fourteen years for periods of eleven to twenty months. All of these children suffered from frequent recurrent respiratory infections, and seventeen of them had attacks of bronchial asthma associated with infections. The author concluded that the results were excellent in eight children, very good in four, inconclusive in one, and one patient was a therapeutic failure. He felt the use of this new type of antigen complex reduced the frequency and severity of respiratory infections in these children and brought about a reduction in the incidence and severity of asthma. Baker,[185] using a staphylococcus bacteriophage lysate aerosol in the treatment of fifty patients with chronic bronchial asthma, noted that twenty cases (44 per cent) obtained excellent results, twenty-one (42

per cent) had good results and only seven cases (14 per cent) obtained fair relief. The author (questionably) concluded that since this type of treatment has afforded sustained systematic relief in every case, that it may be considered valuable as an adjunct to other accepted therapeutic measures in the treatment of intractable bronchial asthma. Sereni and Nonato[186] likewise believed the use of bacterial vaccines to be beneficial in the treatment of asthma in children. Moore and Reed[187] also presented their views on the use of bacterial vaccines in the treatment of asthma and reviewed some of their results with the use of such antigens. Of 3,602 cases studied, 2,520 were treated with a stock vaccine plus other antigens. Nine hundred and twenty-nine patients were treated with stock vaccine alone and 153 were treated with autogenous vaccine. "Those treated with vaccine and other antigens undoubtedly produced the best results. Those treated with stock vaccine alone or with autogenous vaccine alone were 50 to 72 per cent improved. This type of evidence is of questionable significance in the absence of double-blind placebo control comparisons, especially in a disease as variable as asthma." (The reviewers would wholeheartedly endorse this latter statement by Moore and Reed, and for this reason have not felt justified in using bacterial vaccines in the treatment of their patients. In the few reported control studies on the use of bacterial vaccines, some of which are about to be cited, their benefit has not exceeded that produced by placebo injections.)

In contrast to the aforementioned papers, two different controlled studies by Helander[188] and one by Johnstone[189] failed to demonstrate the usefulness of bacterial vaccines in the treatment of bronchial asthma. Helander in a double-blind study of vaccine and a placebo in the treatment of adults found no difference between their therapeutic effects. The respective improvement rates were 68 per cent and 62 per cent. He further compared the effects of administering autogenous vaccine and stock vaccine and could determine no significant difference. It was the author's opinion that the results of his investigations indicated that the effect of bacterial vaccine therapy in infective bronchial asthma is due to psychological factors. In Johnstone's investigations 118 infants and children subject to repeated episodes of asthma associated with respiratory infections were studied. Both vaccine-treated and a control group treated similarly except for omission of bacterial vaccines from hyposensitization therapy were compared before and at the end of a three and a half year period. When the maximum dose of vaccine was administered every twenty-eight days, no statistical differences were observed between the two groups with regard to the following criteria: (1) number of asthmatic episodes per year, (2) the average number of days wheezing per year, (3) average number of days of school missed per year during asthmatic episodes, (4) number of children with 100 per cent, 50 to 100 per cent, or 0 to 50 per cent reduction in number of asthmatic attacks per year. In the vaccine-treated group, the type of vaccine used did not appear to influence the degree of improvement as reflected in the number of asthmatic attacks per year in the last year of the study compared to the year preceding the investigation. The author concluded that within the limits of the study there is no evidence that bacterial vaccine is of any value in the treatment of bronchial asthma.

The beneficial effects of breathing exercises in the treatment of bronchial asthma were described by Miller[190] and also by Walsh.[191] Redford[192] discussed the use of breathing exercises in pulmonary emphysema, but felt that their value was largely subjective. Along these same lines a program of physical conditioning was devised by Scherr and Frankel[193] for a group of

twenty-five asthmatic children in an attempt to improve their respiratory capacity and to develop their initiative and self-confidence. The group met two afternoons each week at the local YMCA under the direction of a physical fitness director. The program included (1) basic techniques of abdominal and diaphragmatic breathing, (2) postural exercises, (3) gymnastics and (4) adaptation conditioning. For the latter purpose, the principles of judo were employed to build up the child's confidence and to train him to handle aggressive situations. The general atmosphere of the program was one of play rather than of medical treatment. The child was further taught to concentrate on improving his own ability rather than on competing with his neighbor. These authors concluded that the program appeared to be beneficial to the participants.

Institutional care for asthmatic children has been established as a helpful therapeutic measure in certain children with intractable asthma. A paper edited by Peshkin and Abramson[194] summarized the discussions at the first national seminar of regional medical consultants of the National Jewish Home for Asthmatic Children in Denver. The subjects discussed at the conference included a history of the development of the Home, its therapeutic program, the clinical results of rehabilitation, the psychiatric aspects at the institutional and private practice level, the significance of allergy in childhood, and breathing exercises for asthmatics. Of particular interest was the presentation of the results of the rehabilitation program. The ratio of boys to girls sent to the Home was two to one: the peak age of onset was at two to three years of age with 64 per cent developing their asthma before six years. Approximately 90 per cent of the children improved if they remained in the Home for two years. Patients with associated perennial allergic rhinitis and chronic eczema, or both, tended to remain unchanged. Considering the selection of patients, the incidence of status asthmaticus at the Home was "strikingly low." Fallers *et al*[195] described a graphic form for assessing the progress and the severity of asthma in children residing at the National Jewish Home for Asthmatic Children at Denver. The form consists principally of the following information: (1) the number of visits to the dispensary for the relief of acute wheezing by nebulization, (2) the frequency and duration of hospitalization for asthma, (3) measurement of pulmonary functions, and (4) the kind and amount of medication used for the control of asthma. Five case histories were also presented to illustrate the application of this form. (The reviewers have also found a similar type of form to be a beneficial aid in the evaluation of patients' progress and response to therapy.)

Steen[196] presented a review of the literature on the effects of climatotherapy and institutional care on asthmatic children. In addition he described the formation, physical, educational and medical facilities, admission procedures and the therapeutic results of the Sahuaro School of the National Foundation for Asthmatic Children. It is the author's belief that one of the beneficial features of this institution is the "ideal" climate in Tucson where the school is located. Of interest were the results achieved in 141 children with intractable asthma who were admitted to the school. Forty-four and six-tenths per cent had excellent results, 19.1 per cent were moderately improved, 29.6 per cent showed fair improvement and only 6.3 per cent had no improvement. There was one death in this group. (It is rather striking that the improvements achieved at the Tucson asthmatic school are quite comparable to those reported from the National Jewish Home for Asthmatic Children and to those observed at the Sunair Home for Asthmatic Children in Tujunga. The program at this Home, under the

direction of Dr. Ernest Heimlich, requires the parents to make weekly visits to the institution. Despite different climates, therapeutic programs and psychological approaches, it is apparent that placing severe intractable asthmatic children, who had failed to respond to conventional treatment, into an asthmatic home has a dramatic beneficial effect on the majority of the children so treated.) In Germany, Kruse[197] stated the frequency of asthma seemed to be increasing among children indicating a need for asthmatic homes. His requirements of such a home included the absence of dust, an altitude of more than 800 meters, and an isolated area. He also stressed the need of a psychological approach in the therapy of these children.

With reference to environmental influences on asthma, Gutmann[198] made some interesting observations on new Iraqi immigrants, previously reported as being healthy, who shortly after their arrival in Israel began to suffer from bronchial asthma. He noted (1) that not all immigrants from Iraq were affected, (2) that the immigrants became ill only in a geographically well-defined area (near Tel Aviv), (3) that the family and individual histories revealed very few allergies in the past, and, finally, (4) that the asthma affected mainly the age group from twenty to forty. The younger age groups, below ten, were almost exempt, while the number of asthmatic children in this age group in Israel is ordinarily high. The author, on the basis of skin tests, incriminated bacterial and mold allergens and speculated on the possible psychogenic origin of the condition. In a footnote, the author stated that the syndrome largely disappeared after the immigrants became integrated into the community. He also made mention of the observation that concentration camp internees, who had previously suffered from asthma, were frequently free of their wheezing during their internment.

The indications for surgery in the treatment of asthma have been discussed by several different authors. Overholt[199] reviewed the historical background of the surgical treatment of asthma. He presented three basic reasons for the surgical exposure of the lung in intractable asthma: (1) to remove or correct a demonstrable structural abnormality which may serve as a "trigger mechanism" to perpetuate spasms, (2) to discover structural changes which may not have been revealed by x-ray, bronchography or bronchoscopy, and (3) to attempt to relieve abnormal bronchospasms by the interruption of nerve control. He presented his results in forty-seven patients treated by surgery over a twelve-year period who were followed postoperatively for at least a year. Six of the patients had succumbed; however, two were followed long enough to determine the effects of surgical intervention. No patients were made worse by the surgical procedures; two patients remained the same; and the remaining patients were "better"—sixteen being completely well with no further asthma. (Considering the severity of the illness and the patients being referred to the thoracic surgeon, it is rather startling that such excellent results were achieved in Overholt's series of patients. In spite of this author's reported excellent results, there is general agreement among allergists that surgical therapy of asthma is rarely a useful therapeutic procedure, the resection of bronchiectatic lesions being an exception. Certainly, surgical intervention for the treatment of asthma in children should not be advised unless clear-cut evidence of localized pulmonary disease is established. Denervation for the treatment of asthma has not been established as an accepted method of therapy, and much further investigation is necessary before this procedure can be generally recommended.)

Prickman and Whitcomb[200] reviewed their experiences in a series of 153 patients with asthma who underwent major surgical procedures in the Mayo Clinic and concluded that the properly prepared asthmatic patient is a good surgical risk. No untoward effects were attributed to their choice of anesthetic agents.

Engstrom and Kraepelien[201] summarized their results with specific desensitization in 110 asthmatic boys and girls ranging in age from one to fifteen years who had been followed for a period of two to four years after the onset of treatment. Improvement was noted in 84 per cent, and the duration of asthma appeared to have no evident effect upon the results. However, the duration of treatment did seem to be of some significance. The longer and more intense the therapy, the better appeared to be the results registered. The authors in their conclusion stressed the significance of specific desensitization in the treatment of asthmatic children. Ryssing[202] reported his results on dust hyposensitization in asthmatic children. Seventy children who showed a positive scratch test to "purified" house dust extract (Boatner-Efron) and who had a positive provocation test, either sniff, inhalation, or both, were studied. After four years of treatment, sixty-three of these children were re-examined and the provocation tests repeated. An appreciable level of tolerance to the provocation test was found in the majority of these patients. It corresponded well to the clinical results. It was not possible to demonstrate any relationship between increase of tolerance and the duration and intensity of treatment and the age at which the treatment was started. The duration of the disease, the child's age, treatment with other extracts or vaccines, or the heredity did not seem to influence the results. In addition, the author urged that in house dust sensitive patients, extensive environmental control measures should be taken to eliminate house dust at the same time. (Owing to the lack of controls, it is difficult to evaluate how much the increased tolerance to dust was due to the hyposensitization.) On the other hand, Quersin[203] in a study of forty-five severe cases of respiratory allergy, concluded that house dust desensitization is of doubtful value and suggested more efforts be placed on environmental control of dust.

X-ray therapy of bronchial asthma was recommended by Ilyinskiy and Ruchimovitch.[204] They treated fifty-seven children and obtained a complete cure in two cases and improvement in thirty-eight of the subjects. (Observers are almost unanimous in their opinion that this type of therapy should now be avoided in the treatment of asthma.)

Dickstein[205] surveyed our present knowledge of enzymes useful in the treatment of asthma and briefly summarized some of his own experiences with the use of intramuscular trypsin and chymotrypsin. Of ninety-eight patients treated, twenty-eight obtained marked relief as evidenced by loosening of the secretions and lessening of dyspnea. Nineteen had moderate relief, and fifty-one had no relief. Of interest was the occurrence of severe allergic reactions in seven of the patients (asthma, generalized urticaria, swelling of the entire extremity) and six additional subjects had moderate local reactions at the site of the injection. The author concluded that these agents were most effective in patients with secondary infection and especially in children. Patients with acute asthma and chronic emphysema were not generally helped. (In view of the rather frequent allergic and local reactions observed with trypsin and chymotrypsin, the difficulty of evaluating the clinical effectiveness of such preparations and the difference of opinion among investigators using these agents, the reviewers have hesitated to use

these enzymes and believe their administration should be limited to investigative studies.)

Two papers have appeared which stressed some of the serious complications that can occur in the treatment of status asthmaticus. Saier, Hecker and Krupp[206] described a patient who had developed severe shock as a complication of status asthmaticus, which was treated with vasopressor amine and hydrocortisone. In the management of seriously ill asthmatic patients, Koelsche *et al*[207] stated there are five major therapeutic objectives: (1) environmental control, (2) rest, (3) control of coughing, (4) liquefaction of the sputum, and (5) the control of anoxemia. Details in achieving the five objectives are presented, as well as the administration of steroids in the seriously ill asthmatic subjects. Finally, the authors concluded "the management of asthma remains a problem of many facets. It is not too difficult to outline didactically a program of treatment, but in practice all of us will encounter cases that will tax our therapeutic ingenuity to the limit. Finally, medicines afford only symptomatic relief and none is good enough to overcome the bad effects of poor environmental control."

An editorial[208] on asthma in childhood further stressed the importance of a multi-therapeutic approach.

The relationship of tonsillectomy to asthma and allergic rhinitis has been discussed by several authors. Lerner and Markow[209] reported their observations on seventy patients who had been subject to tonsillectomy and who had either asthma or some form of allergic rhinitis. After surgical intervention, only two did well while none of the others was benefited, and many developed new or increased signs of allergic disorders. Mitolo[210] also concluded that a tonsillectomy serves no useful purpose in the treatment of bronchial asthma.

Clein[211] presented a somewhat different viewpoint. He reviewed his experiences with 930 children, including 283 allergic patients who had their tonsils and adenoids removed "for definite indication." About 50 per cent of the allergic children required this operation because their allergy predisposed to excessive growth of lymphoid tissue. He felt that about one-third of the present tonsillectomies could be avoided if the patients were properly diagnosed and treated for allergy early in their disease. Clein further warned against doing tonsillectomies during the summer months since it would not only aggravate the child's present symptoms but could predispose him to the development of asthma.

References

130. Oliver, T. K., Jr., Shaw, R. S. and Wheeler, W. E.: Pulmonary ventilation in infants under one year of age. A.M.A. J. Dis. Child., 97:774, 1959.
131. Levin, S. J.: The management of the acute attack of asthma in childhood. A.M.A. J. Dis. Child., 97:432, 1959.
132. McGovern, J. P.: Therapy of acute attacks of asthma in infants and children. J.A.M.A., 169:20, 1959.
133. Logan, G. B.: Treatment of the child having asthma. Minnesota Med., 41:831, 1958.
134. Fontana, V. J.: Treatment of infective bronchial asthma in children. New York J. Med., 58:2525, 1958.
135. Mueller, H. L.: The use of drugs in the management of asthma in children. Quart. Rev. Pediat., 13:5, 1958.
136. Unger, L., Wolf, A. A., Johnson, J. H. and Unger, D. L.: Management of bronchial asthma in children. J. Pediat., 52:539, 1958.
137. Segal, M. S.: Current status of therapy in bronchial asthma. J.A.M.A, 169: 1063, 1959.

138. Krantz, J. C.: The pharmacologic approach to bronchial asthma. Bull. School Med. Univ. Maryland, 43:58, 1958.
139. Pearson, R. S. B.: Asthma. Brit. M. J., 905 (Oct. 11) 1958.
140. Ratner, B.: The use and abuse of drugs in the treatment of asthma in children. Pediatrics, 23:781, 1959.
141. Reif, A. E. and Mitchell, C.: Size analysis of water aerosols. Ann. Allergy, 17:157, 1959.
142. Schiller, I. and Lowell, F.: An appraisal of oral and aerosolized methylphenidate hydrochloride (Ritalin) in obstructive pulmonary disease. J. Allergy, 29:151, 1958.
143. Zohman, L. and Williams, M. H., Jr.: Comparative effects of aerosol bronchodilators on ventilatory function. J. Allergy, 29:72, 1958.
144. Beck, G. J.: A new effective method of nebulizing bronchodilator aerosols: Clinical and physiological effects. Dis. Chest, 33:607, 1958.
145. Goldstein, M. M., Ottinger, E. O., Hapner, I.: Physiologic studies with the medihaler—isoproterenol in bronchospastic diseases—alcoholic preparation —non-alcoholic preparation. Ann. Allergy, 15:626, 1957.
146. Leslie, A. and Simmons, D. H.: Evaluation of the bronchodilator, Caytine (JB-251). Am. J. M. Sc., 234:321, 1957.
147. Little, R. C. and Poettler, H. W.: The comparative effect of bronchodilator agents administered by inhalation: A controlled clinical study. Am. J. M. Sc., 236:336, 1958.
148. Settel, E.: A new broncholytic drug. JB251 (Caytine). Am. Pract. & Digest Treat., 8:1249, 1957.
149. Christensen, J. M., Valasek, F. E., Tainter, M. L.: Ethylnorepinephrine. A unique bronchodilator. Am. Pract. & Digest Treat., 9:916, 1958.
150. Dornhorst, A. C. and Herxheimer, A.: Effects of isoprenaline isomers in man. Lancet, 2:722, 1958.
151. Tuft, H. S.: Evaluation of choline theophyllinate in the management of chronic asthma of childhood. Ann. Allergy, 15:420, 1957.
152. Pengelly, C. D. R., and Brockbank, W.: Oral theophylline compounds in chronic asthma. A blind clinical trial. Brit. M. J., 867, 1959.
153. Cass, L. J. and Frederik, W. S.: A new xanthine derivative. New York J. Med., 58:2391, 1958.
154. Schluger, J., McGinn, J. T. and Burbank, B.: Treatment of the acute asthmatic attack with an oral alcohol-water solution of theophylline (elixophyllin). Am. J. M. Sc., 234:28, 1957.
155. Frank, D. E.: Spirometric evaluation of a water-alcohol-soluble theophylline (elixophylline) in acetylcholine-induced asthma. Antibiotic Med., 6:338. 1959.
156. MacLaren, W. R.: Elixophyllin in the treatment of acute and chronic asthma: clinical evaluation and pulmonary function studies. Ann. Allergy, 17:729, 1959.
157. Spielman, A. D.: Comparative effectiveness of an alcohol-water solution of theophylline (elixophyllin), alcohol-water solution, and theophylline-water solution for the oral treatment of acute bronchial asthma. J. Allergy, 30:35. 1959.
158. Cohen, N. J.: Aminophylline poisoning. Ann. paediat., 191:16, 1958.
159. Couch, R. D., Franz, M. and Forney, R. B.: Aminophylline poisoning. Report of a case with complete pathologic and toxicologic finding. Am. J. Clin. Path., 30:435, 1958.
160. Bacal, H. L., Linegar, K., Denton, R. L., and Gourdeau, R.: Aminophylline poisoning in children. Canad. M. A. J., 80:6, 1959.
161. Lilien, B. B.: Toxic reactions from the overdose of rectal aminophylline suppositories in asthmatic infants and young children: Case report. J. Newark Beth Israel Hosp., 8:351, 1957.
162. Levin, S. J.: Aminophylline (theophylline) in pediatrics. Quart. Rev. Pediat., 14:107, 1959.
163. Forbes, J., Wise, L.: Expectorants and sputum viscosity. Lancet, 2:767, 1957.
164. Hillis, B. R. and Stein, L.: The assessment of expectorant drugs. Scottish M. J., 3:252, 1958.
165. Fein, B. T.: Bronchial asthma in children and adults; treated by the prophylactic use of an iodide-containing bronchodilator drug. Texas J. Med., 53:848, 1957.
166. Allport, R. B.: Ipecac is not innocuous. A.M.A. J. Dis. Child., 98:787, 1959.
167. Baum, G. L., Schotz, S. A., Gumpel, R. C. and Osgood, C.: The role of chlor-

promazine in the treatment of bronchial asthma and chronic pulmonary emphysema. Dis. Chest., 32:574, 1957.
168. Tuft, H. S.: Prochlorperazine as an aid in the treatment of bronchial asthma. Ann. Allergy, 17:228, 1959.
169. Michelson, A. L., and Lowell, F. C.: The limited use of chlorpromazine in bronchial asthma. Am. J. M. Sc., 234:31, 1957.
170. Grater, W. C.: Prophylaxis of recurring infection in children with asthma by the use of tetracycline. Am. Pract. & Digest Treat., 9:249, 1958.
171. Fishman, A. E.: Sulfonamide therapy in the prevention of asthma associated with infection. Ann. Allergy, 17:588, 1959.
172. Lewis-Faning, E. and Davies, W.: A controlled trial of continuous oral penicillin therapy in asthmatic children during five winter months. Acta allergol., 13:67, 1959.
173. Editorial: Antibiotic prophylaxis. New England J. Med., 257:1048, 1957.
174. Petersdorf, R. G., Curtin, J. A., Hoeprich, P. D., Peeler, R. N. and Bennett, I. L.: A study of antibiotic prophylaxis in unconscious patients. New England J. Med., 257:1001, 1957.
175. Sanchez-Ubeda, R., Fernand, E. and Rousselot, L. M.: The value of penicillin and streptomycin as postoperative prophylaxis—a study of 511 cases. New England J. Med., 259:1045, 1958.
176. Barnes, J., Pace, W. G., Trump, D. S. and Ellison, E. H.: Prophylactic postoperative antibiotics. A.M.A. Arch. Surg., 79:190, 1959.
177. Petersdorf, R. G. and Merchant, R. K.: A study of antibiotic prophylaxis in patients with acute heart failure. New England J. Med., 260:565, 1959.
178. Dragsted, P. J. and Hansen, P. F.: Treatment of bronchial asthma with N-mustard gas. Acta allergol., 13:180, 1959.
179. Herxheimer, H.: Atropine cigarettes in asthma and emphysema. Brit. M. J., 167 (Aug. 15) 1959.
180. Kusunoki, N., Toshida, K., Takagi, Z., Yoshida, T., Ogate, S., Maseki, T. and Suzuki, H.: Long term treatment of bronchial asthma with PAS. 54th Annual Meeting, Jap. Soc. Int. Med., 1957.
181. Dann, S., Brown, F. R., Baustista, I. A., Spielman, A. D. and Kupperman, H. S.: The effectiveness of scopolamine n-methyl bromide (pamine bromide) in the treatment of bronchial asthma. Ann. Allergy, 17:562, 1959.
182. Frank, D. E.: The effect of drugs in acetylcholine-induced bronchial obstruction. Ann. Allergy, 17:207, 1959.
183. Schiller, I. W., Lowell, F. C. and Alman, J. E.: The use of color-coded tablets in the clinical appraisal of two established bronchodilator preparations and N-[β-(10-phenothiazinyl) propyl] trimethylammonium benzene chloride. J. Allergy, 29:293, 1958.
184. Gundy, J. E.: Acellular bacterial antigen complex (Hoffmann) in the treatment of children with recurrent respiratory infections and infectious asthma. J. Pediat., 51:516, 1957.
185. Baker, A. G.: Treatment of chronic bronchial asthma. Aerosol of staphylococcus bacteriophage lysate as an adjunct to systemic hyposensitization. Am. Pract. & Digest Treat., 9:591, 1958.
186. Sereni, F. and Nonato, M.: The efficacy of autovaccine treatment in asthmatic syndromes in children. Clin. pediat., 39:624, 1957.
187. Moore, M. W. and Reed, C. E.: Clinical evaluation of stock respiratory vaccine in the treatment of bronchial asthma. Ann. Allergy, 17:722, 1959.
188. Helander, E.: Bacterial vaccines in the treatment of bronchial asthma. Acta allergol., 13:47, 1959.
189. Johnstone, D. E.: Study of the value of bacterial vaccines in the treatment of bronchial asthma associated with respiratory infections. Pediatrics, 24:427, 1959.
190. Miller, W. F.: Physical therapeutic measures in the treatment of chronic bronchopulmonary disorders: Methods for breathing training. Am. J. Med., 24:929, 1958.
191. Walsh, R. J.: Corrective breathing exercises for patients with bronchial asthma and obstructive pulmonary emphysema. Ann. Allergy, 16:410, 1958.
192. Redford, J. B.: Effects of breathing exercises on pulmonary emphysema. Arch. Phys. Med., 39:357, 1958.
193. Scherr, M. S. and Frankel, L.: Physical conditioning program for asthmatic children. J.A.M.A., 168:1996, 1958.
194. Peshkin, M. M. and Abramson, H. A.: First national seminar of regional medical consultants. Ann. Allergy, 16:473, 1958.
195. Fallers, C. J., Bekarogulu, M. and Peshkin, M. M.: A graphic form as a progress index of asthmatic patients. Ann. Allergy, 17:434, 1959.

196. Steen, W. B.: Rehabilitation of children with intractable asthma. Ann. Allergy, 17:864, 1959.
197. Kruse, F.: The necessity of homes for asthmatic children. Deutsche Gesundh., 12:1329, 1957.
198. Gutmann, M. J.: An investigation into environmental influences in bronchial asthma. Ann. Allergy, 16:536, 1958.
199. Overholt, R. H.: Pulmonary denervation and resection in asthmatic patients. Ann. Allergy, 17:534, 1959.
200. Prickman, L. E. and Whitcomb, F. F.: The decreasing hazard of surgical procedures on patients with asthma. Dis. Chest., 35:30, 1959.
201. Enstrom, I. and Kraepelien, S.: Specific desensitization in bronchial asthma in childhood. Acta paediat., 46:81, 1957.
202. Ryssing, E.: The prognosis in allergy to house dust in asthmatic children elucidated by provocation experiments. Acta paediat., 46:419, 1957.
203. Quersin, C.: Les allergies respiratoires chez l'enfant. Acta allergol., 13:19, 1959.
204. Ilyinskiy, P. I. and Ruchimovitch, G. S.: Roentgenotherapy of bronchial asthma in children. Pediatriya, 9:88, 1957.
205. Dickstein, B.: Enzyme lysis of asthmatic sputum. A review and progress report. Ann. Allergy, 17:784, 1959.
206. Saier, M., Hecker, S. and Krupp, M.: Treatment of status asthmaticus complicated by vasomotor collapse. J. Allergy, 30:61, 1959.
207. Koelsche, G. A., Carryer, H. M., Peters, G. A. and Henderson, L. L.: Management of the seriously ill asthmatic. J.A.M.A, 166:1541, 1958.
208. Editorial: Asthma in childhood. Canad. M. A. J., 80:833, 1959.
209. Lerner, M. F. and Markow, H.: Tonsillectomy and allergy. New York J. Med., 59:2888, 1959.
210. Mitolo, G. R.: Relationships between diseases of the tonsils and bronchial asthma in children. Minerva pediat., 9:305, 1957.
211. Clein, N. W.: Allergy and the tonsil problem in children. Northwest Med., 58:845, 1959.

(To be continued in the January Issue)

MODERN EDUCATION AND HUMAN VALUES

A man is free, or he enjoys liberty, in the proportion to which his life is governed by his own choice. Freedom is not doing as one pleases, but doing as one chooses. And choice itself is a matter of degree; for it may be wide or narrow, deep or shallow. Choice is narrowed by ignorance, habit or obsession; it is broadened by knowledge, spontaneity and reflection. Choice is also confined by circumstances beyond his control. Choice is vain, or is mere idle wishing, when the chosen isn't possible; choice is real and effective when its means lie within its reach. The greater part of human knowledge serves the purpose of making choices effective, whatever they may be. It provides men with tools, and extends their control of circumstances. Technology and organized history reduce man's dependence on his fiscal environment; the socialized state reduces his dependence on his social environment. Before these agencies circumstance becomes more plastic to the will; man becomes to a diminishing extent the victim of circumstances, whether hostile and different forces of nature or his own tyrannies of social custom and authority.—RALPH BARTON PERRY, *When is Education Liberal?*, Pitcairn-Crabbe Foundation Lecture Series, Vol. III, Pittsburgh University, University of Pittsburgh Press, 1950.

Index to Volume 18

AUTHOR AND SUBJECT INDEX

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

Z

BOOK REVIEWS

BOOKS OF INTEREST

EDITORIAL

HISTORICAL DOCUMENTS

IN MEMORIAM

MISCELLANEOUS

NEWS ITEMS

PAPERS OF INTEREST

PRESIDENT'S PAGE

PROGRESS IN ALLERGY

ANNALS OF ALLERGY

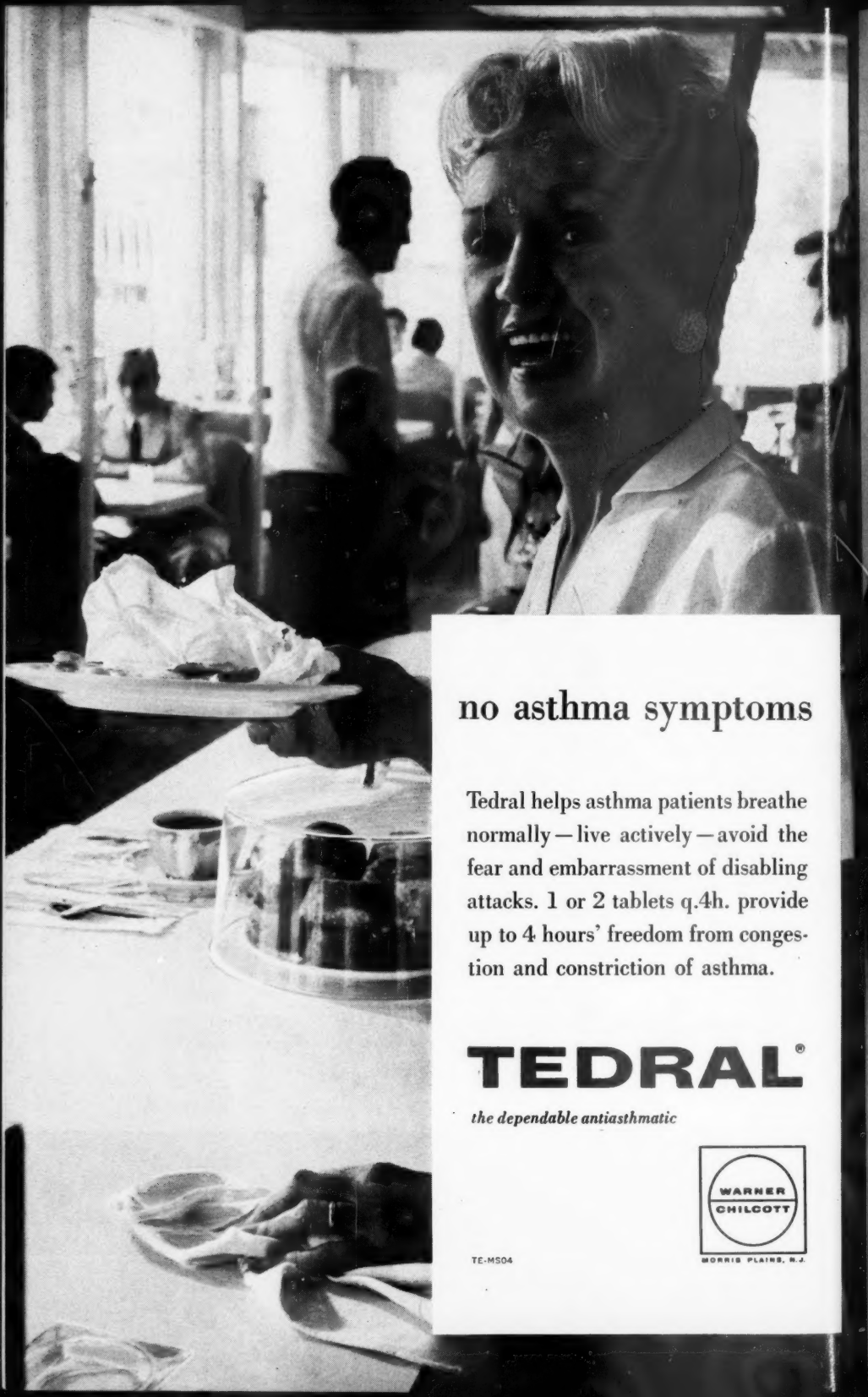
olume 18, Number 12 December, 1960

Graduate Instructional Course — March 12-14, 1961

Seventeenth Annual Congress — March 15-17, 1961

Statler-Hilton Hotel
Dallas, Texas

Published Monthly by
THE AMERICAN COLLEGE OF ALLERGISTS
Established 1942



no asthma symptoms

Tedral helps asthma patients breathe normally—live actively—avoid the fear and embarrassment of disabling attacks. 1 or 2 tablets q.4h. provide up to 4 hours' freedom from congestion and constriction of asthma.

TEDRAL®

the dependable antiasthmatic

WARNER CHILCOTT

TE-MS04

MORRIS PLAINS, N.J.

ANNALS *of* ALLERGY

Published monthly as the official publication of The American College of Allergists by the Bruce Publishing Company, 2642 University Avenue, Saint Paul 14, Minnesota, U. S. A.

CONSULTANT EDITORIAL BOARD

Anaphylaxis and Rheumatic Fever

EDWARD E. FISCHEL, M.D., Director of Medicine, The Bronx Hospital, New York, New York

Cardiology

J. WILLIS HURST, M.D., Professor of Medicine, Emory University, Atlanta, Georgia

JOSEPH E. F. RISEMAN, M.D., Assistant Clinical Professor of Medicine, Harvard Medical School, Boston, Massachusetts

Chemical Mechanisms in Allergy and Related Fields

MANUEL H. GORIN, Ph.D., Member, American Chemical Society, and Society of Automotive Engineers; Fellow, New York Academy of Sciences, San Francisco, California

Clinical Chemistry

J. A. HANCOCK, Ph.D., Professor of Chemistry, Texas Western College of the University of Texas, El Paso, Texas

FELIX HAUROWITZ, Ph.D., Professor of Chemistry, Indiana University, Bloomington, Indiana

Dermatologic Allergy

GEORGE H. CURTIS, M.D., Associate Professor of Dermatology, Frank E. Bunts Educational Institute and Cleveland Clinic Foundation, Cleveland, Ohio

OTIS FIELD JILLSON, M.D., Staff Dermatologist, Hitchcock Clinic, Hanover, New Hampshire

JOHN D. KRAFCHUK, M.D., Assistant Professor of Medicine, Tulane University School of Medicine, New Orleans, Louisiana

Hematology

CLAUDE-STARR WRIGHT, M.D., Head, Division of Hematology, Department of Medicine, Medical College of Georgia, Augusta, Georgia

Immunology

MERRILL W. CHASE, Ph.D., Associate Member of the Rockefeller Institute, New York, New York

JULES FREUND, M.D., Chief, Laboratory of Immunology, National Institute of Allergy and Infectious Disease, Bethesda, Maryland

WILLIAM J. KUHNS, M.D., Associate Professor of Pathology, University of Pittsburgh Medical School, Pittsburgh, Pennsylvania

SIDNEY RAFFEL, M.D., Executive and Professor, Department of Medical Microbiology, Stanford University, Stanford, California

Meteorology and Climatology

KONRAD J. K. BUETTNER, Ph.D., Associate Professor, Department of Meteorology and Climatology, University of Washington, Seattle, Washington

Otolaryngology

NOAH D. FABRICANT, M.D., Clinical Assistant Professor of Otolaryngology, University of Illinois College of Medicine, Chicago, Illinois

Pathology

GORDON R. HENNIGAR, M.D., Associate Professor of Pathology, Medical College of Virginia, Richmond, Virginia

Pharmacognosy

C. C. ALBERS, Ph.D., Professor of Pharmacognosy, The University of Texas, College of Pharmacy, Austin, Texas

Psychiatry

RIVES CHALMERS, M.D., Atlanta Psychiatric Clinic, Atlanta, Georgia

Pulmonary Function

DAVID CUGELL, M.D., Physician-in-Charge, Pulmonary Function Laboratory, Northwestern University Medical School, Chicago, Illinois

Radiology

TED F. LEIGH, M.D., Associate Professor of Radiology, Emory University School of Medicine, Atlanta, Georgia

MAX RITVO, M.D., Director, Department of Radiology, and Roentgenologist-in-Chief, Boston City Hospital, Boston, Massachusetts

Thoracic Surgery

JEROME R. HEAD, M.D., Associate Professor of Surgery, Northwestern University Medical School, Chicago, Illinois

Toxicology

HARRY W. HAYS, Ph.D., Director, Toxicological Information Center, National Academy of Sciences, Washington, D. C.

Urology

HAROLD P. MCDONALD, M.D., Chief, Department of Urology, St. Joseph's Infirmary, Atlanta, Georgia

The American College of Allergists

OFFICERS—1960-1961

GILES A. KOELSCHE, M.D. ..... Rochester, Minnesota
President

PHILIP M. GOTTLIEB, M.D. ..... Philadelphia, Pennsylvania
President-Elect

STANISLAUS H. JAROS, M.D. ..... Harlingen, Texas
First Vice President

SAM H. SANDERS, M.D. ..... Memphis, Tennessee
Second Vice President

ELOI BAUERS ..... Minneapolis, Minnesota
Executive Vice President

HOWARD G. RAPAPORT ..... New York, New York
Secretary

JOHN D. GILLASPIE, M.D. ..... Boulder, Colorado
Treasurer

BOARD OF REGENTS

		Term Expires
Maurice C. Barnes, M.D.	Waco, Texas	1961
Lester L. Bartlett, M.D.	Pittsburgh, Pa.	1962
William H. Browning, M.D.	Shreveport, La.	1963
Cecil Collins-Williams, M.D.	Toronto, Canada	1961
R. Dale Dickson, M.D.	Topeka, Kansas	1962
M. Coleman Harris, M.D.	San Francisco, Calif.	1962
Clifford H. Kalb, M.D.	Milwaukee, Wis.	1963
Delbert J. Parsons, M.D.	Springfield, Ohio	1961
Lamar B. Peacock, M.D.	Atlanta, Ga.	1963
Giles A. Koelsche, M.D. (President)	Rochester, Minn.	

BOARD OF DIRECTORS

Cecil M. Kohn, M.D. ..... Kansas City, Missouri
Chairman

Giles A. Koelsche, M.D. ..... Rochester, Minnesota
Vice Chairman

Philip M. Gottlieb, M.D. ..... Philadelphia, Pennsylvania
Stanislaus H. Jaros, M.D. ..... Harlingen, Texas
Maurice C. Barnes, M.D. ..... Waco, Texas

new, low-dosage FLEET® THEOPHYLLINE RECTAL UNIT

provides therapeutic blood levels in bronchial or cardiac asthma with reduced side effects

advantages of Fleet Theophylline Rectal Unit

over suppositories — Water-soluble form assures more uniform absorption over a wider mucosal area . . . without irritation. Avoids slow and erratic absorption of suppositories, which are especially hazardous in children.[1,2]

over oral therapy — Avoids oral xanthine side effects (gastric irritation, nausea, vomiting)[3] and loss of drug effectiveness through hepatic metabolism.[4]

over parenteral therapy — Obviates potential danger and inconvenience of xanthine injection.[1]

over higher potency products — Recent clinical work indicates that "the amounts of theophylline required for relief of bronchospasm are lower than previously thought necessary" and side effects are decidedly reduced with the lower dosage.[5] Early studies[6] also demonstrate rapidity and duration of relief.

ADMINISTRATION: Usual dose—contents of a single unit as often as the physician may direct. FLEET® THEOPHYLLINE Rectal Unit contains 0.3125 Gm. theophylline monoethanolamine in 37 ml. aqueous solution, delivering 0.250 Gm., a 3¾-gr. dose.

AVAILABILITY: FLEET® THEOPHYLLINE Rectal Unit is supplied in a prescription package of 6 individual ready-to-use units. **Also available for patients requiring greater concentrations:** CLYSMATHANE® Disposable Rectal Unit containing 0.625 Gm. theophylline monoethanolamine in prescription package of 6 individual ready-to-use units. This product delivers 0.5 Gm., a 7½-gr. dose.

1. Ridolfo, A. S., and Kohlstaedt, K. G.: Am. J. M. Sc. 237:585, May, 1959. 2. Nolke, A. C.: J. A. M. A. 161:693, June 23, 1956. 3. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, Macmillan, 1955, p. 349. 4. Blumenthal, L. S., and Fuchs, M.: Am. J. Gastroenterol. 33:189, Feb., 1960. 5. Prince, H. E.; Jackson, R. H.; Etter, R. L.; Raymer, W. J., and Moreland, F. B.: Theophylline Blood Level Studies Following the Rectal Administration of Theophylline Monoethanolamine, to be published. 6. Jackson, R. H.; Prince, H. E., and McGivney, F.: Ann. Allergy 18:620, June, 1960.

Complete information on request.

C. B. FLEET CO., INC. Lynchburg, Virginia

for "special-problem" patients...
when corticosteroid therapy is indicated

Aristocort (triamcinolone)

unsurpassed "general purpose" steroid outstanding for "special purpose" therapy

in allergic respiratory disorders

Aristocort®

Triamcinolone LEDERLE

UNSURPASSED "GENERAL-PURPOSE" STEROID
OUTSTANDING FOR "SPECIAL-PURPOSE" THERAPY

ARISTOCORT Triamcinolone has long since proved its *unsurpassed efficacy and relative safety* in treating allergic respiratory disorders, including bronchial asthma. Clinical evidence has now shown that ARISTOCORT is also highly valuable for "special-problem" patients – asthmatic and others – who, because of certain complications, were hitherto considered poor candidates for corticosteroids.

for example:

PATIENTS WITH IMPENDING CARDIAC DECOMPENSATION

In contrast to most of its congeners, ARISTOCORT is not contraindicated when edema is present or when cardiac decompensation impends.[1]

PATIENTS WITH EMOTIONAL AND NERVOUS DISORDERS

Triamcinolone did not produce psychic disturbances or insomnia.[2]

PATIENTS WHOSE APPETITES SHOULD NOT BE STIMULATED

Among patients treated with ARISTOCORT, there was less appetite stimulation, especially in those who had previously gained weight on long-term therapy with other steroids.[3]

PATIENTS WITH HYPERTENSION

There was no blood pressure increase in any patient treated for bronchial asthma, and in some, blood pressure fell. Of these, three had been hypertensive.[4]

References:

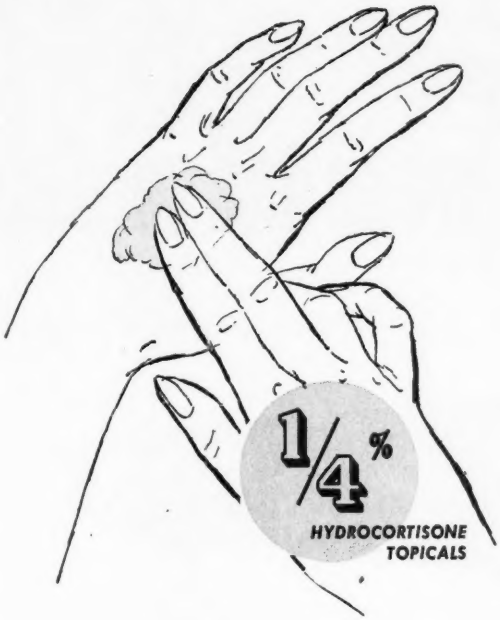
1. McGavack, T. H.; Kao, K. Y. T.; Leake, D. A.; Bauer, H. G., and Berger, H. E.: *Am. J. M. Sc.* 236:720 (Dec.) 1958.
2. McGavack, T. H.: *Nebraska M. J.* 44:377 (Aug.) 1959.
3. Friedlaender, S., and Friedlaender, A. S.: *Antibiotic Med. & Clin. Ther.* 5:315 (May) 1958.
4. Sherwood, H., and Cooke, R. A.: *J. Allergy* 28:97 (March) 1957.

Precautions: Collateral hormonal effects generally associated with corticosteroids may be induced. These include Cushingoid manifestations and muscle weakness. However, sodium and potassium retention, edema, weight gain, psychic aberration and hypertension are exceedingly rare. In the treatment of allergic respiratory disorders, dosage should be individualized and kept at the lowest level needed to control symptoms. Dosage should not exceed 36 mg. daily without potassium supplementation. Drug should not be withdrawn abruptly. Contraindicated in herpes simplex and chicken pox.

Supplied: Scored tablets – 1 mg. (yellow); 2 mg. (pink); 4 mg. (white); 16 mg. (white).
Also available – syrup, parenteral and various topical forms.

Lederle

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, N.Y.



economical maintenance therapy in atopic dermatoses

Long-term use of topical steroids has real advantages in most eczematous diseases; but this means daily applications for many weeks and even months after visible signs of the disease have disappeared.[1] The 0.25% hydrocortisone topicals afford therapeutic effectiveness at a fraction of the cost.[2]

CORT-DOME®
(pH 4.6)
0.25% micronized hydrocortisone alcohol in the exclusive ACID MANTLE® vehicle.

NEO-CORT-DOME™
(pH 4.6)
0.25% micronized hydrocortisone alcohol plus 5.0 mg./Gm. of neomycin sulfate in the exclusive ACID MANTLE vehicle.

CARBO-CORT™
(pH 4.6)
0.25% micronized hydrocortisone alcohol plus 3.0% liquor carbonis detergens in the exclusive ACID MANTLE vehicle.

CORT-QUIN™
(pH 4.5)
0.25% micronized hydrocortisone alcohol plus 1.0% diiodohydroxyquinoline in the exclusive ACID MANTLE vehicle.

COR-TAR-QUIN™
(pH 5.0)
0.25% micronized hydrocortisone alcohol plus 1.0% diiodohydroxyquinoline and 2.0% liquor carbonis detergens in the exclusive ACID MANTLE vehicle.

DOME

The exclusive ACID MANTLE vehicle potentiates the ingredients in DOME preparations . . . restores and maintains the normal protective acidity of the skin...and facilitates healing.

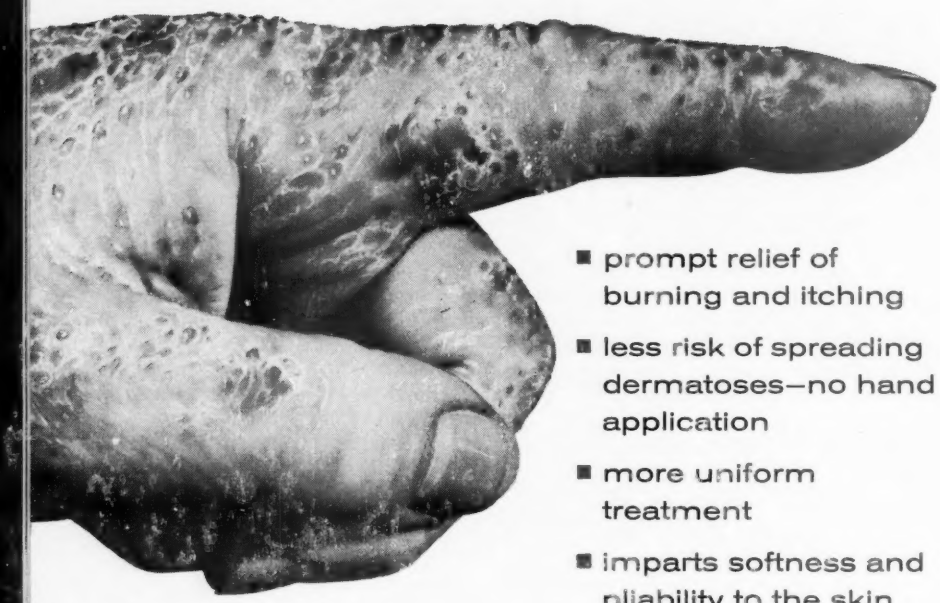
Available as CREMES in 1 oz. tubes, 4 oz. and 1 lb. jars; and as LOTIONS in 4 fl. oz. bottles.

These preparations are also available with higher hydrocortisone concentrations.

1.) Stoughton, R. B.: Report To The Council; Steroid Therapy In Skin Disorders, J.A.M.A. 170:1311-1315 (July 11) 1959. 2.) Goodman, H.: Concentration of Topical Medications Dispersed in Evaporating Vehicles with Particular Reference to Hydrocortisone Alcohol, Clin. Med. 6:781-784 (May) 1959.

World Leader In Dermatologicals
DOME CHEMICALS INC.
New York / Los Angeles

NOW in contact dermatitis
for fast relief...press and release



- prompt relief of burning and itching
- less risk of spreading dermatoses—no hand application
- more uniform treatment
- imparts softness and pliability to the skin
- efficient spray from any angle

plus

- mg. for mg. the most active steroid
- optimal steroid concentration
- the quick-acting broad activity of neomycin

TOPICAL AEROSOL

Decaspray®

DEXAMETHASONE–NEOMYCIN SULFATE

the new touch in topical therapy

Dosage: Apply to the affected area 2 or 3 times a day. Dosage may be adjusted up or down depending upon severity of the disorder. Hold aerosol container approximately 6 inches from the affected area and allow a one- or two-second spray for each 4-inch-square area to be treated (i.e., one second for an area the size of the back of the hand). Each second of spray dispenses approximately 0.075 mg. of dexamethasone and 0.375 mg. of neomycin sulfate.

Supplied: In 90-Gm. seamless, pressurized cans, containing 10 mg. dexamethasone and 50 mg. of neomycin sulfate (equivalent to 35 mg. neomycin base).

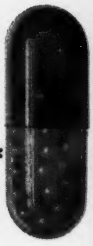
Additional information on DECASPRAY is available to physicians on request.

DECADRON and DECASPRAY are trademarks of Merck & Co., INC.

MSD MERCK SHARP & DOHME
Division of Merck & Co., INC., West Point, Pa.

Upjohn The Upjohn Company Kalamazoo, Michigan

Hard filled capsules in bottles of 30.



4 mg.

Medrol* Medules†

pH-patterned slow release...

not here at pH 1.2

In the relatively acid medium of the fasting stomach, Medules are kept essentially intact by their special pH-sensitive coating (about 5% of Medrol content released in 2 hours at pH 1.2).

but here at pH 7.5

In the environment of the duodenum (at pH of approximately 7.5) 90% to 100% of the Medrol content is released within 4 hours.

...means gradual steroid absorption

135 tiny doses mean smoother** steroid therapy

(**So smooth and protracted that even among rheumatoid arthritis patients "morning stiffness in a great majority of these patients just doesn't exist any more. They wake up comfortable." Iuppa, N. V.: Curr. Therap. Res. 2:177 (June) 1960.)

Medrol hits the disease, but spares the patient

*Trademark, Reg. U. S. Pat. Off.—methylprednisolone, Upjohn

†Trademark

Super-Oiled

Oilatum® Soap

hypoallergenic cleanser

for tender, sensitive skin.

- Super-oiled (not super-fatted) to minimize "drying"
- 600% higher content of unsaturated oils than other cleansers
- Rich, oil-laden lather, even in hard water
- Ideal for pediatric and geriatric use
- Available scented or unscented

COMPLEMENT
DON'T COMPLICATE
SKIN TREATMENT

Super-moisturized

Oilatum® Cream

(new improved formula)

for dry, thirsty skin.

- An oil-in-water emulsion buffered to pH 5.5
- Leaves "the film that breathes" . . . retards moisture loss
- Contains highly unsaturated vegetable oils . . . no lanolin or mineral oil
- Cosmetically pleasant . . . scented or unscented

You can recommend STIEFEL Oilatum Cream with confidence for symptomatic therapy of dry, tender or sensitive skin, lanolin or alkali-sensitivity, ichthyosis, winter itch, wind burn and similar etiologic entities.

STIEFEL
LABORATORIES, INC.
Oak Hill, New York
Canada: Winley Morris, Montreal
Logical Dermatologicals—Since 1847

Samples & literature of Oilatum Soap & Oilatum Cream sent on request.

teamwork in a teaspoon

Each teaspoonful of POLARAMINE *Expectorant provides four therapeutic effects for more complete, rapid and effective relief of the coughs and complications associated with your patients' allergic respiratory disorders.*

Swollen, congested mucous membranes are returned to normal rapidly, gently; dry, unproductive coughing is relieved; and further allergic response and its manifestations are reduced.

Each 5 cc. teaspoonful of POLARAMINE Expectorant contains:
2 mg. POLARAMINE (dexchlorpheniramine) Maleate
20 mg. d-Isoephedrine Sulfate
100 mg. Glyceryl Guaiacolate
Supply: 16 oz. bottles.

Schering

POLARAMINE®
expectorant

when sensitive patients sample forbidden fruit...

BENADRYL®

antihistaminic-antispasmodic

provides simultaneous dual control of the allergic attack · *affords antihistaminic action* that relieves gastrointestinal, cutaneous, and respiratory symptoms · *exerts antispasmodic effect* for effective relief of colicky pain, nausea, and vomiting.

BENADRYL Hydrochloride (diphenhydramine hydrochloride, Parke-Davis) is available in a variety of forms including: Kapseals,® 50 mg. each; Kapseals, 50 mg., with ephedrine sulfate, 25 mg.; Capsules, 25 mg. each; Elixir, 10 mg. per 4 cc.; and for delayed action, Emplets,® 50 mg. each. For parenteral therapy, BENADRYL Hydrochloride Steri-Vials,® 10 mg. per cc.; and Ampoules, 50 mg. per cc. 27369

PARKE-DAVIS

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

B.A.C.

For the Prevention and Treatment of Recurring Upper Respiratory Infections and Infectious Asthma

B.A.C.—Acellular Bacterial Antigen Complex—although derived from bacteria, is not a cellular vaccine. Prepared by the special Hoffmann process of coprecipitation, it provides the specific protective substances of the bacterial cell *plus* the toxins and metabolites. Standardized to uniform potency, B.A.C. is an acellular, water-clear solution, essentially free of sensitizing extraneous components, and is not liable to deterioration on keeping, with resultant loss of antigenic properties.

B.A.C. avoids the pitfalls of antibiotic therapy—Stimulates immune body formation, avoids development of resistant bacteria and superinfections and liability to allergic reactions.

B.A.C. provides important antigens lacking in cellular vaccines—Vaccines lack important specific surface antigenic factors and are deficient in exotoxins and other antigenic metabolites.

B.A.C. combines the essential immunogenic factors for maximum immunologic response.

B.A.C. acts to improve the natural defense mechanisms—The action of B.A.C. is immunologically natural, namely, stimulation of the host's defense against bacterial invaders.

B.A.C. affords prompt, effective and safe therapy—Controlled clinical studies[1-5] in both children and adults have consistently shown favorable response in more than 80 per cent of cases of upper respiratory infection and infectious asthma. Significant side effects have been rarely noted and are eliminated by dilution of the antigen.

B.A.C. is available in multiple dose vials in several different combinations for broad-spectrum immunization. Complete information on B.A.C. preparations, clinical experience, and dosage will be supplied on request.

1. Spielman, A. D.: New York J. Med. *55*:1603 (June 1) 1955.
2. Shinefield, M. A.: New York J. Med. *56*:1466 (May 1) 1956.
3. Dalven, J., and Romano, F. J.: New York J. Med. *57*:1748 (May 15) 1957.
4. Gundy, J. E.: J. Pediat. *51*:516 (Nov.) 1957.
5. Spielman, A. D.: A.M.A. Arch. Otolaryng. *67*:204 (Feb.) 1958.

Hoffmann Laboratories, Inc.
666 Broadway, Paterson 4, N. J.

'ACTIFED'®

Decongestant / Antihistamine

THE POTENTIATED DECONGESTANT

provides symptomatic relief of nasal congestion and rhinorrhea of allergic or infectious origin

Many patients whose symptoms are inadequately controlled by decongestants or antihistamines alone respond promptly and favorably to 'ACTIFED'.

'ACTIFED' contains:	in each Tablet	in each tsp. Syrup
'Actidil'® brand Triprolidine Hydrochloride	2.5 mg.	1.25 mg.
'Sudafed'® brand Pseudoephedrine Hydrochloride	60 mg.	30 mg.

safe and effective for patients of all ages suffering from upper respiratory tract congestion

DOSAGE

	TABLETS	SYRUP (5 cc. tsp.)	
Adults and older children	1	2	three times daily
Children 4 months to 6 years of age	½	1	
Infants through 3 months	–	½	

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

Bathsheba at her toilet
by Rembrandt.

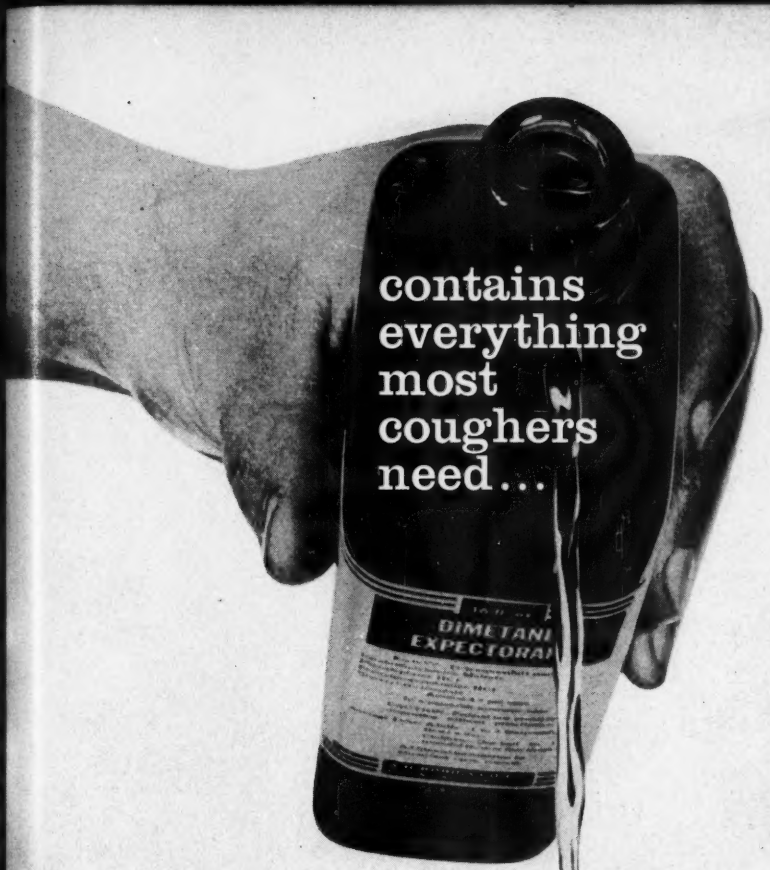
a pleasant way to treat dry, itchy skin

Alpha-Keri™

water-dispersible, antipruritic oil for the bath or shower

Alpha-KERI makes dry skin feel soft and smooth immediately. It effectively deposits a uniform, partially-occlusive oil film over the entire skin area. Alpha-KERI lubricates the skin, relieves itching and restores the protective action of natural skin oils lost by the action of water, weather and detergents. It moisturizes the skin and also helps to retain moisture by retarding evaporation of water. Alpha-KERI contains: Kerohydric®, brand of dewaxed, oil-soluble, keratin-moisturizing fraction of lanolin, mineral oil, and a special nonionic emulsifier which provides the right amount of water dispersibility for optimum coverage of the skin with emollient oils. Alpha-KERI oil may be used in the bath, in the shower, for sponge bathing and for infant baths. It can also be used for skin cleansing where soap is contraindicated. Alpha-KERI oil is tinted an attractive green color and pleasantly scented. Bottles of 8 fl. oz. *Write for samples and literature.*

Westwood Pharmaceuticals, Buffalo 13, New York



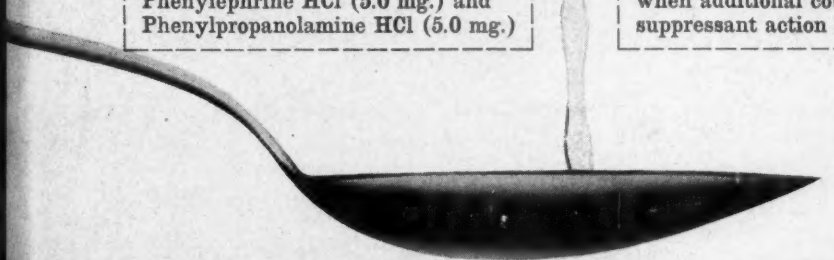
Each 5 cc. (1 teaspoonful) contains:

DIMETANE—
(Parabromdylamine Maleate, 2.0 mg.)
the antihistamine
most likely to succeed

two highly approved
decongestants
Phenylephrine HCl (5.0 mg.) and
Phenylpropanolamine HCl (5.0 mg.)

Glyceryl Guaiacolate (100.0 mg.)
the expectorant that works best
—increases respiratory tract
fluid almost 200%

IN DIMETANE EXPECTORANT-DC
—added dihydrocodeinone
1.8 mg./5 cc.
when additional cough
suppressant action is needed



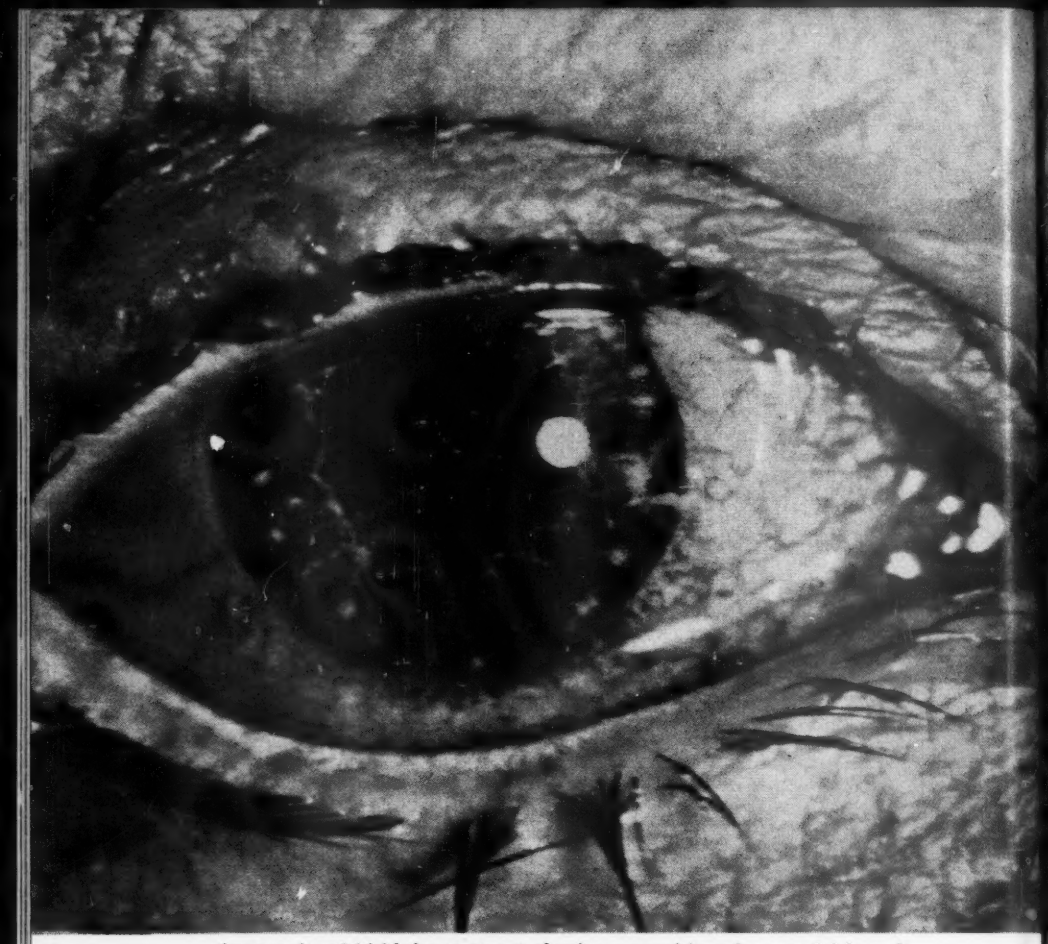
for less frequent, more productive cough

DIMETANE® EXPECTORANT

DIMETANE® EXPECTORANT-DC

Robins

A. H. ROBINS CO., INC., RICHMOND 20, VIRGINIA

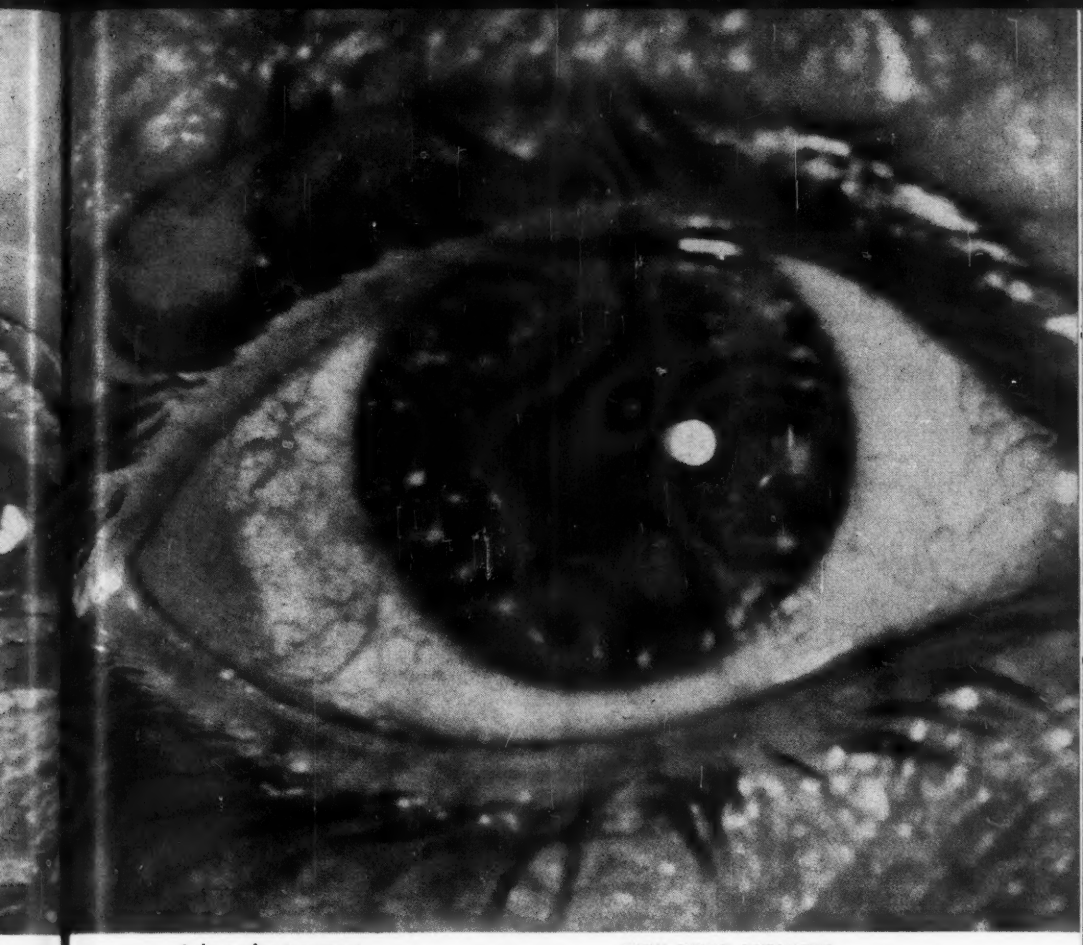


Acute conjunctivitis[1] before treatment, showing engorged irregular superficial vessels

NOW...the true solution for fast anti-inflammatory response and no irritating steroid particles

- mg. for mg. the most active steroid topically—up to 40 times the potency of hydrocortisone
- optimal not minimal steroid concentration in true solution for peak effectiveness . . . maximal contact at the site of the lesion
- quick-acting broad antimicrobial activity when infection threatens recovery
- superior patient comfort—no stinging, no irritating particles, bland carrier

1. Gordon, D. M.: Scientific Exhibit, American Medical Association, Annual Meeting, San Francisco, 1958.



4 days after treatment ACTUAL CLINICAL PHOTOGRAPHS

OPHTHALMIC SOLUTION

NeoDecadron*

DEXAMETHASONE 21-PHOSPHATE—NEOMYCIN SULFATE

INDICATIONS: Trauma—mechanical, chemical or thermal; conjunctival, corneal, or uveal tract inflammation involving the anterior segment; allergy; blepharitis.

DOSAGE: NeoDECADRON Ophthalmic Solution (0.1%)—One drop 4-6 times daily.
NeoDECADRON Ophthalmic Ointment (0.05%)—Applied 3-4 times daily.

In severe or sight-threatening conditions, the frequency of administration may be increased. Systemic therapy with DECADRON Tablets may be prescribed adjunctively.

PRECAUTION: Steroid therapy should never be employed in the presence of tuberculosis or herpes simplex.

Additional information is available to physicians on request.

*NeoDECADRON and DECADRON are trademarks of Merck & Co., Inc.

Product	Steroid Concentration	active ingredients: Dexamethasone 21-Phosphate (as the disodium salt)	active ingredients: Neomycin Sulfate	Supplied
NeoDECADRON Ophthalmic Solution	0.1%	1 mg./cc.	5 mg./cc. (equivalent to 3.5 mg. neomycin base)	5 cc. (¼ oz.) sterile dropper-bottles
DECADRON Phosphate Ophthalmic Solution	0.1%	1 mg./cc.	—	5 cc. (¼ oz.) sterile dropper-bottles
NeoDECADRON Ophthalmic Ointment	0.05%	0.5 mg./Gm.	5 mg./Gm. (equivalent to 3.5 mg. neomycin base)	3.5 Gm. (⅛ oz.) tubes
DECADRON Phosphate Ophthalmic Ointment	0.05%	0.5 mg./Gm.	—	3.5 Gm. (⅛ oz.) tubes

MERCK SHARP & DOHME
Division of Merck & Co., Inc. • Philadelphia 1, Pa.

for women sensitive to eye cosmetics

NEW AR-EX HYPO-ALLERGENIC

Now from the laboratories of AR-EX comes a complete line of hypo-allergenic eye beauty aids. Tests have proved that women sensitive to usual eye cosmetics can safely use AR-EX Hypo-Allergenic Eye Make-Up. In a glamorous array of fashion-fresh shades.

SUBTRACTIVES MAKE THE DIFFERENCE

AR-EX MASCARA
Contains no lacquer, soap, turpentine, perfume.

AR-EX EYE SHADOW
Contains no indelible dyes, lanolin, cocoa butter, or perfume.

AR-EX EYE PENCIL
Contains no indelible dyes, lanolin or perfume.

All AR-EX eye cosmetics are available "Unscented" only—and are odorless.

Send for supply of folders for patients.

mascara
eye pencil
eye shadow

HYPO-ALLERGENIC COSMETICS

Formulated so all women can use fine cosmetics

AR-EX PRODUCTS CO., 1036 W. VAN BUREN ST., CHICAGO 7, ILL.

LOGICAL NEW DERMATOLOGICAL HELPS

solve the mystery of Acne Therapy

Brāsivol has a gentle abrasive action that attacks the acne lesion simply and directly. It maintains the mild desquamation so essential to the successful acne regime. Helps open plugged pores, reduce pustules and blackheads, control oiliness. Helps minimize postacne scars. The patient simply applies Brāsivol abrasive cleanser 2 or 3 times daily, and rinses. Ritual helps relieve urge to squeeze pimples. Cooperation is enhanced because results are readily seen and felt. Safety and success are supported in over 10 years of clinical studies on thousands of acne cases. Brāsivol (pat. pend.) contains precisely sized abrasive particles (fused aluminum oxide) and hexachlorophene 1%, in a detergent and drying base. Compatible with other therapeutic measures.

Write for starter samples and literature

STIEFEL®

LOGICAL DERMATOLOGICALS—since 1847

Oak Hill, New York

CANADIAN REPRESENTATIVE:
WINLEY-MORRIS CO., LTD., Montreal 29, Quebec

Brāsivol Fine *Brāsivol Medium* *Brāsivol Rough*

Brāsivol is supplied in 3 abrasive grades, permitting gradual intensification of abrasive action as the acne improves. Also, Brāsivol Base (abrasive free) now available for acute inflammatory cases.

Jars of Brāsivol Base 5 oz.; Brāsivol Fine 5¾ oz.; Brāsivol Medium 6¼ oz.; Brāsivol Rough 7 oz.

Brāsivol®

ABRASION THERAPY FOR ACNE

in certain other countries Brāsivol is available as DENCO-BRAS™

REFERENCES:
SAPERSTEIN, R. B.: Treatment of Acne with Long Term Continuous Abrasion. Presented at 107th Annual Meeting of A.M.A.
REES, R. B.; BENNETT, J. H.; GREENLEE, M. R.: Newer Drug Treatment in Dermatology, Cal. Med.; 91:1, July 1959.
SULZBERGER, M. B. & WITTEN, V. H.: The Management of Acne Today. Med. Clinics of No. America, 43:3, May 1959.

Contents for December, 1960

IN CHRONIC BRONCHITIS,
CHRONIC ASTHMA AND EMPHYSEMA

HIGHER THEOPHYLLINE BLOOD LEVELS MORE EFFECTIVE BRONCHODILATATION

less gastric distress—for uncomplicated therapy

Choledyl produces far less gastrointestinal irritation than oral aminophylline. In a study of 200 geriatric patients chronically ill with pulmonary emphysema, bronchitis and asthma, Choledyl was found to be "extremely well tolerated."*

greater solubility—for enhanced theophylline blood levels

Up to 75% higher theophylline blood levels than oral aminophylline—provides superior bronchodilatation: relieves bronchospasm—reduces coughing and wheezing—increases vital capacity—reduces incidence and severity of acute attacks—decreases need for secondary medication.

*Simon, S. W.: Ann. Allergy *14*:172-180 (March-April) 1956.

CHOLEDYL®

the choline salt of theophylline

brand of oxtriphylline

WARNER CHILCOTT
MORRIS PLAINS, N.J.

6P04

betters breathing . . . decreases wheezing

NOW FOR NEW CONTROL OF

Asthma

℞ **EPHOXAMINE®**

Bronchodilator/tranquilizer

WITH FREEDOM FROM...

- **excitation**
- **gastric upset**
- **urinary retention**
- **respiratory depression**

"Ephoxamine has been found to be a *highly useful asthmalytic* preparation, which seems to be effective when the usual, oral asthmalytics are not."[1]

"Ephoxamine is a *highly effective* drug for maintenance therapy in chronic bronchial asthma."[3]

"Ephoxamine is *well tolerated* and has not been productive of any significant side-effects to date."[3]

EACH SCORED TABLET CONTAINS: 50 mg. Phenyltoloxamine DHC
25 mg. Racephedrine HCl

DOSAGE: Adults: 1 to 2 tablets every 4 hours
Children: (6 to 12 years) one half adult dosage

1. Swarts, H., "Ephoxamine in the Symptomatic Treatment of Bronchial Asthma," Current Therapeutic Research, 1:93:1959. 2. Flothow, M. W., "Ephedrine and Antihistamine Combined Treatment in Allergies," J. of Med. Soc. of N.J. 56:733:1959. 3. Swarts, H., "Ephoxamine as Maintenance Drug Therapy in Chronic Bronchial Asthma: a Preliminary Report," Applied Therapeutics 1:3:1960.

SPENCER LABORATORIES, INCORPORATED
MORRISTOWN, NEW JERSEY

Seventeenth Annual Congress

and

Graduate Instructional Course

of

The American College of Allergists

will be held

March 12-17, 1961

at the

Statler Hilton Hotel

Dallas, Texas

Plan now to attend this important meeting. Learn firsthand the advanced diagnostic and therapeutic procedures currently employed by specialists in your field of practice.

Preregistration is earnestly recommended.

a breathing spell from asthma

Quadrinal*

a rapid way to clear the airway

- **stops wheezing**
- **increases cough effectiveness**
- **relieves spasm**

In chronic disorders associated with obstructed respiration, the dependable antispasmodic and expectorant action of Quadrinal rapidly clears the bronchial tree. Patients breathe more easily and acute episodes of bronchospasm are often eliminated. Quadrinal is well tolerated, even on prolonged administration. The potassium iodide in Quadrinal provides an expectorant of time-tested effectiveness and safety.

Indications: Bronchial asthma, chronic bronchitis, pulmonary fibrosis, pulmonary emphysema.

Quadrinal Tablets, containing ephedrine HCl (24 mg.), phenobarbital (24 mg.), 'Phyllicin'* (theophylline-calcium salicylate) (130 mg.), **and potassium iodide** (0.3 Gm.).

Also available—
a new Quadrinal dosage form with taste-appeal for all age groups:
fruit-flavored QUADRINAL SUSPENSION (1 teaspoonful = 1/2 Quadrinal Tablet)

KNOLL PHARMACEUTICAL COMPANY, ORANGE, NEW JERSEY

*Quadrinal, Phyllicin®

Science for the world's well-being™

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

IN BRIEF

ATARAXOID combines the tension-relieving effects of hydroxyzine with the anti-allergic action of prednisolone, a well-established corticosteroid, for superior control without *unexpected* side effects.

INDICATIONS: Allergic states, including chronic bronchial asthma and severe hay fever; rheumatoid arthritis, collagen diseases, and related conditions; other musculoskeletal disorders (myositis, fibrositis, bursitis, etc.); and allergic/inflammatory diseases of the skin and eyes.

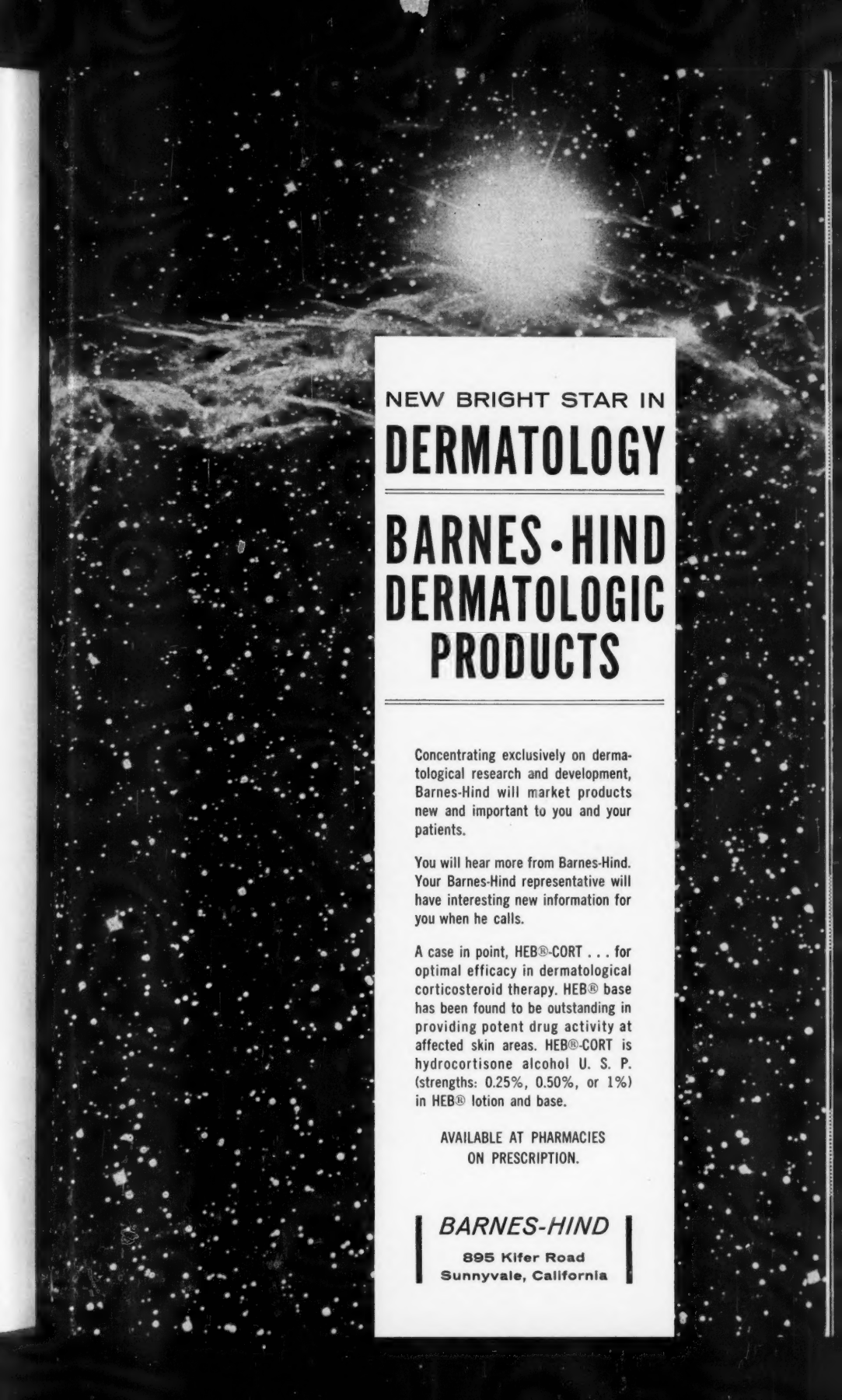
ADMINISTRATION AND DOSAGE: ATARAXOID dosage varies with individual response. Clinical experience suggests the following daily dosage: *Initial therapy*—4-6 ATARAXOID *5.0* Tablets. *Maintenance*—1-4 ATARAXOID *5.0* Tablets or 2-8 ATARAXOID *2.5* Tablets. After initial suppressive therapy, gradual reduction of prednisolone dosage should begin and continue until the smallest effective dose is reached. Prescribe in divided doses, after meals and at bedtime.

SIDE EFFECTS: Prednisolone may produce all of the side effects common to other corticosteroids. As with other corticosteroids, insomnia, mild hirsutism, moonface and sodium retention have occurred. Osteoporosis may develop after long-term corticosteroid therapy.

PRECAUTIONS AND CONTRAINDICATIONS: Usual corticoid precautions should be observed. Incidence of peptic ulcer may increase on long-term prednisolone therapy. However, therapy has often been maintained for long periods without adverse effects. Contraindicated in infectious disease including active tuberculosis (except under close supervision), peptic ulcer, certain infections of the cornea, such as dendritic keratitis, superficial punctate keratitis, epidemic keratoconjunctivitis, and in patients with emotional instability. Caution is indicated in the treatment of patients with severe cardiovascular disease, and in some cases sodium restriction and potassium supplementation must be considered.

SUPPLIED: As green, scored ATARAXOID *5.0* Tablets, containing 5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride and blue, scored ATARAXOID *2.5* Tablets containing 2.5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride.

More detailed professional information available on request.


NEW BRIGHT STAR IN
DERMATOLOGY
BARNES·HIND
DERMATOLOGIC
PRODUCTS
Concentrating exclusively on dermatological research and development, Barnes-Hind will market products new and important to you and your patients.
You will hear more from Barnes-Hind. Your Barnes-Hind representative will have interesting new information for you when he calls.
A case in point, HEB®-CORT . . . for optimal efficacy in dermatological corticosteroid therapy. HEB® base has been found to be outstanding in providing potent drug activity at affected skin areas. HEB®-CORT is hydrocortisone alcohol U. S. P. (strengths: 0.25%, 0.50%, or 1%) in HEB® lotion and base.
AVAILABLE AT PHARMACIES
ON PRESCRIPTION.
BARNES-HIND
895 Kifer Road
Sunnyvale, California

Good grooming is part of the job for the perfect secretary. By prescribing Allercreme Hypo-allergenic Cosmetics to the businesswomen in your practice, you can help them maintain a glow of healthy beauty despite dry, sensitive or allergic skin. Allercreme Hypo-allergenic Cosmetics cleanse, protect, lubricate, refresh and make-up every skin type . . . and each preparation is as pharmaceutically-safe and free of irritants as modern science makes possible. Write for prescription folders and samples.

Allercreme® HYPO-ALLERGENIC COSMETICS

DIVISION OF TEXAS PHARMACAL CO. SAN ANTONIO, TEXAS, U.S.A.

In Canada — Omega Laboratories, Ltd., Montreal and Toronto
In Cuba — Laboratories Amedin, S. A., Habana
In Venezuela — Salus, C. A., Caracas

Index to Advertisers

Please Patronize Our Advertisers First, and Mention ANNALS OF ALLERGY *When Writing Our Advertisers*

SUS-PHRINE

aqueous epinephrine suspension 1:200

whenever
EPINEPHRINE
is
indicated

1
INJECTION
DOES THE
WORK OF
TWO

Sus-Phrine presents epinephrine in a unique combination of aqueous suspension and solution. A *single* subcutaneous injection does the work of both a 1:1000 aqueous injection and an oil suspension intramuscular injection.

One injection of Sus-Phrine provides—

IMMEDIATE RELIEF—of the total 1:200 epinephrine concentration, 20% is in solution—gives the same immediate relief as a 1:1000 aqueous injection.

PROLONGED RELIEF—the remaining 80% in suspension is absorbed slowly, exerting a continuous effect over a period of 8 to 12 hours.

Sus-Phrine is the epinephrine preparation of choice wherever it has been given a clinical trial. Over thirty published papers affirm this.* Sus-Phrine is especially useful in pediatric practice.

SUPPLIED: 0.5 cc. ampuls, packages of 12, for use in office and home calls. 5 cc. multidose vials for use in hospital emergency wards.

**Write for detailed literature and bibliography.*

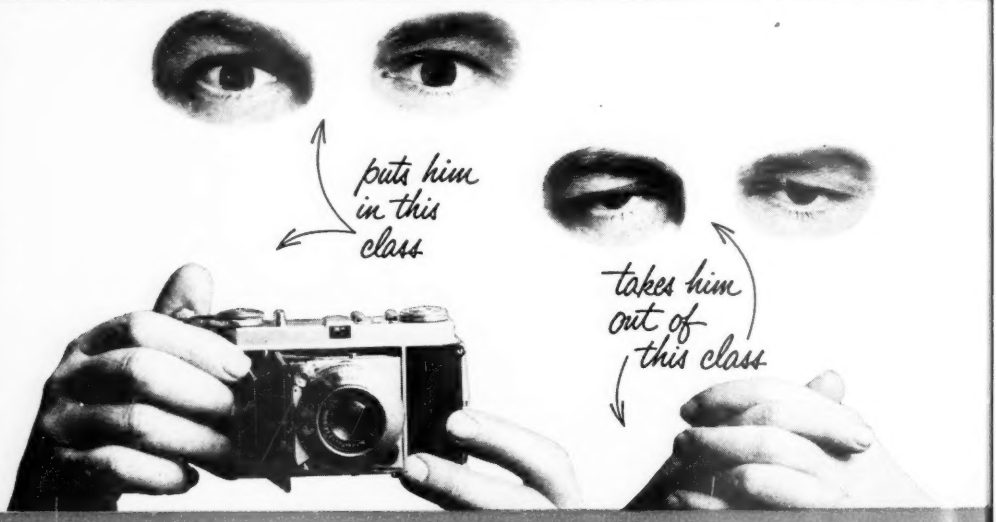
Brewer
Est. 1852

BREWER & COMPANY, INC.
Worcester 8, Massachusetts

WHAT THIS **NEW** ANTIHISTAMINE DOES FOR YOUR PATIENT

ANTI= ALLERGIC & SIDE EFFECTS

Twiston*



Twiston — the **NEW "TAILOR-MADE" ANTIHISTAMINE** — has been designed to provide full symptom-control—yet side effects, particularly drowsiness, are negligible or absent.

- *No toxicity* has been reported with TWISTON
- Keeps patient *symptom-free*, alert—with unusually *low dosage*

available dosage forms:
Tablets TWISTON, 2 mg.
Tablets TWISTON R-A, 4 mg. (Repeat Action Tablets)

usual dosage:
TWISTON
Adults: 1 to 2 tablets t.i.d. or q.i.d.
Children: 1/2 to 1 tablet t.i.d. or q.i.d.
TWISTON R-A
Adults: 1 tablet q. 8 to 12 hours.

McNEIL **McNEIL LABORATORIES, INC., Philadelphia 32, Pa.** *Trade-mark U. S. Patent Pending